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Summary of Evidence Base

- Our searches identified one systematic review, one retrospective database study, and one prospective cohort study that addressed this question.
  - The systematic review includes 11 studies examining opioid treatment agreement and urine drug testing strategies.[1]
    - Review authors' analysis concluded that weak evidence exists supporting these risk mitigation strategies as effective for reducing opioid misuse among patients receiving chronic opioid therapy (Quality of evidence ratings for outcomes reported in this systematic review: Low to Very low)
    - Conclusions are supported by two meta-analyses (N=426 and N=500, respectively)
  - One retrospective database study investigated the interaction between the degree of individual- and facility-level guideline-recommended opioid care at Veterans Health Administration facilities and patients' risk of attempting suicide.[2]
    - Study authors reported that, at the facility level, adherence to strong care and management practices, including regular drug screening and specialized substance use treatment, was associated with decreased risk of patients attempting suicide. Conversely, high sedative and SNRI co-prescription rates were associated with increased suicide attempt risk among patients receiving long-acting opioid therapy. (Quality of evidence rating: Moderate)
    - Subgroup analysis of patients with comorbid SUD found similar patterns between strong guideline adherence and patients' decreased suicide risk. (Quality of evidence rating: Moderate)
  - One prospective study examined the efficacy of using clinical pharmacist-led guidance teams to provide structured, comprehensive management and risk mitigation services to patients receiving chronic opioid therapy to treat chronic pain due to cancer.[3]
    - Study authors report that, compared to standard of care, treatment directed by clinical pharmacist-led guidance teams was associated with better pain management, improved patient quality of life, and reduced adverse event rates. therapy (Quality of evidence ratings for outcomes reported in this study: Very low)
- Our searches did not identify any systematic reviews that comprehensively addressed the efficacy of other risk mitigation strategies, nor did we locate any eligible randomized controlled trials investigating any risk mitigation strategies of interest among this patient population. The quality of the identified evidence base ranged from Very Low to Moderate, often due to significant methodological issues among included studies.

Overview of Evidence Base

Our searches identified one systematic review (SR), one retrospective database study, and one prospective cohort study that addressed this question. The systematic review included 11 studies (5 prospective cohort studies and 6 retrospective cohort studies).[1] These studies evaluated the efficacy of opioid treatment agreements (OTA), routine urine drug testing (UDT), or a combination of the two strategies for reducing opioid misuse among patients receiving chronic opioid therapy for chronic pain management.[1] The retrospective database study investigated the effectiveness of guideline-based opioid therapy management and risk reduction practices for reducing suicide attempts among patients receiving chronic opioid therapy from various Veterans Health Administration (VHA) facilities during a single fiscal year.[2] The prospective cohort study investigated various benefits associated with using pharmacist-led guidance teams to provide comprehensive opioid therapy and risk mitigation services to patients administered chronic opioid therapy for cancer pain management.[3] Excluded studies and the reasons for exclusion appear in Table 4, Appendix C.

Study Quality Rating

Starrels et al. rated the studies included in their systematic review as very low to low quality.[1] The main methodological concerns noted by the review authors included imprecise sample size, incomplete data, sampling bias, and use of measures with questionable clinical relevance among original papers.

We assessed the quality (methodological risk of bias) of individual studies using criteria developed by the U.S. Preventive Services Task Force (USPSTF). The retrospective study by Im et al.[2] has a quality rating of fair; although it was very large and adjusted for multiple relevant variables in its statistical analyses, it did not adjust for all relevant potential confounders. The quality of the prospective study by Chen et al.[3] is rated as poor, as the authors documented issues with data collection consistency, lack of randomization, and lack of blinding.

Overview of Study, Patient, and Intervention Characteristics

The systematic review by Starrels et al.[1] evaluated 11 studies, enrolling 2,655 patients. All studies enrolled adult patients, with the majority of patients aged 40 to 65 years old. The percentage of enrolled female patients ranged from 4% to 59%. In 10 of 11 studies, authors investigated the risk mitigation efficacy of OTA. Two studies each compared OTA to control (standard care) and OTA and routine UDT to historical control. OTA and UDT were investigated with no comparator in two studies, as was OTA and routine UDT with monthly visits, and OTA and UDT with monthly visits. A single study compared routine UDT without a comparator.[1] All included studies evaluated patients receiving at least 3 months of chronic opioid therapy.

Im et al.[2] retrospectively queried data from 487,462 adult veterans receiving chronic short- or long-acting opioid therapy from the VHA during the 2010 fiscal year. Female patients comprised 6.5% of the study population. All patients received at least a minimum 90-day supply of opioid medication, with facility-based protocols varying from low routing drug screening and no or minimal specialty dependence and rehabilitation services, to frequent drug screening and specialized care and management.[2] Study authors compared veterans suicide attempt risk rates and statistical interactions with facility-based protocols over a 12 month period.

Chen et al.[3] enrolled 542 adult patients with diagnosed chronic cancer pain; study authors did not report gender demographics. The study explored the efficacy of comprehensive treatment, including pain management education and drug monitoring and counseling, to standard of care. Comprehensive interventions were provided by trained clinical physician-led guidance teams for a 6-month study period.

Outcomes and Synthesis of Results

Opioid Misuse

Each of 11 studies in the Starrels et al.[1] systematic review reported opioid misuse as a primary outcome. Four studies reported results using absolute risk reduction percentages; the remainder reported misuse rate data. The review authors conducted meta-analysis of 2 absolute risk reduction studies comparing OTA to control, and 2 absolute risk reduction studies comparing OTA and routine UDT to a historical control group; both analyses favored the experimental risk mitigation tools for reducing patients' opioid misuse (absolute risk reduction The 7 remaining studies reported misuse rate data, with single study rates between 3% and 43%; however, due to assessment tool and classification heterogeneity issues, review authors were unable to conduct meta-analyses with these studies.[1]

Suicide Attempts

Im et al.[2] concluded that veterans receiving short- or long-acting opioid therapy at VHA facilities with increased drug screening had a decreased risk of suicide attempts; the authors reported similar findings among subgroups of veterans with comorbid SUD who received treatment from VHA facilities with higher levels of specialized SUD or rehabilitation treatment resources. In addition, veterans on long-acting opioids at VHA facilities with more follow-up after new prescriptions had a decreased risk of suicide attempts. In contrast, multivariate logistic regression analyses found increased suicide attempt risk among veterans receiving long-acting opioid therapy at VHA facilities with higher rates of sedative or SNRI co-prescription.[2]

Adverse Events, Pain Relief, and Quality of Life

The prospective study by Chen et al.[3] reported data from three outcome classes (adverse events, pain relief, and quality of life). For each outcome, the authors found that cancer patients receiving clinical physician-led guidance team-led treatment had superior outcomes, with fewer adverse events, better pain management, and improved quality of life.[3]

Overall Quality of Evidence Rating

The overall quality of evidence ratings ranged from Very low to Moderate across different outcomes. Low ratings reflected the limitations of Fair- to Poor-quality studies, while Very Low ratings reflected additional serious study limitations. Moderate ratings were assigned to a fair-quality study that had serious limitations but relatively large effect sizes. Very low to Low evidence supported the efficacy of OTA, alone or with UDT, for reducing drug misuse among chronic pain patients administered opioid therapy.[1] Moderate quality evidence supported the relationship between facilities' adherence to recommended guidelines for opioid therapy management and risk mitigation and a reduced risk of suicide attempts among veterans receiving chronic opioid therapy at VHA facilities.[2] Very low quality evidence supported the efficacy of clinical pharmacist-guided opioid therapy delivery teams for improving treatment-related adverse events, pain management, and quality of life among patients with chronic pain.[3]

Table 1. Overall Assessment of Quality of Evidence Base

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
OTA Versus Control/Usual Care								
Opioid misuse risk reduction	1 SR (Starrels et al. 2010[1])	OTA vs. control (2 retrospective cohort studies; 426 patients)	Absolute risk reduction = 20.9% to 22.9%; maximum 95% CI: 10.6% to 31.2% (2 studies; n=426) Favors OTA	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
OTA and Routine UDT Versus Historical Control								
Opioid misuse risk reduction	1 SR (Starrels et al. 2010[1]	OTA and routine UDT vs. control (2 prospective cohort studies; 500 patients)	Absolute risk reduction = 6.5% to 8.6%; maximum 95% CI: 1.3% to 12.8% (2 studies; n=500) Favors OTA and routine UDT	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Very low
Facility-level Adherence to Guideline-recommended Care and Opioid Management Protocols								
Attempted suicide risk	1 retrospective database study (Im et al. 2015[2])	Chronic short-acting opioid therapy managed with more or less frequent routine drug screening (393.657 patients)	OR=0.2, 95% CI: 0.1 to 0.3 More routine drug screening is associated with decreased risk of suicide attempt	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Attempted suicide risk	1 retrospective database study (Im et al. 2015[2])	Chronic short-acting opioid therapy managed with more or less frequent routine drug screening SUD (47,771 patients)	OR=0.3, 95% CI: 0.2 to 0.6 More routine drug screening is associated with decreased risk of suicide attempt	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Attempted suicide risk	1 retrospective database study (Im et al. 2015[2])	Long-acting opioid therapy with more or less frequent routine drug screening, follow-up, or co-prescription (93,805 patients)	Drug Screening: OR=0.3, 95% CI: 0.2 to 0.6 More routine drug screening is associated with decreased risk of suicide attempt Follow-up: OR=0.2, 95% CI: 0.0 to 0.7 More follow-up is associated with decreased risk of suicide attempt Co-prescription: OR=20.3, 95% CI: 1.1 to 382.2 More co-prescribing is associated with increased risk of suicide attempt	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Attempted suicide risk	1 retrospective database study (Im et al.[2])	Long-acting opioid therapy and comorbid SUD with or more or less frequent rehabilitation services or co-prescription (13,732 patients)	Rehabilitation services: OR=0.3, 95% CI: 0.1 to 0.9 More rehabilitation services are associated with decreased risk of suicide attempt Sedative co-prescription: OR=30.2, 95% CI: 1.1 to 829.3 SNRI co-prescription: OR=62.2; 95% CI: 2.2 to 1,769.3 More co-prescribing is associated with increased risk of suicide attempt	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Clinical Pharmacist-led Guidance Teams Versus Control/Usual Care								
Adverse events	1 prospective cohort study (Chen et al. 2014[3])	Clinical Pharmacist-led Guidance Team-managed opioid therapy vs. control (543 patients)	Gastrointestinal AEs (CPGT vs. Control): Constipation: 42.1% vs. 51.4%; OR=0.73 (95% CI: 0.61 to 0.93); p=0.041 Nausea: 15.1% vs. 22.8%; OR=0.62 (95% CI: 0.32 to 0.99); p=0.028 Vomiting: 15.7% vs. 22.1%; OR=0.58 (95% CI: 0.41 to 0.89); p=0.035 Psychological AEs (CPGT vs. Control): Delirium: 7.3% vs. 11.2%; OR=0.78 (95% CI: 0.56 to 0.98); p=0.088 Excessive sedation: 4.1% vs. 6.7%; OR=0.65 (95% CI: 0.47 to 0.78); p=0.062 Itchy skin: 13.4% vs. 12.4%; OR=1.05 (95% CI: 0.87 to 1.26); p=0.289 Addiction: 0% vs. 1.8% All AEs favor CPGT intervention	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Pain management	1 prospective cohort study (Chen et al. 2014[3])	Clinical Pharmacist-led Guidance Team-managed opioid therapy vs. control (543 patients)	Pain Management (numeric pain scale; CPGT vs. Control): Bone: 3.1±0.9 vs. 4.2±1.3; OR=0.86 (95% CI: 0.61 to 1.32); p=0.038 Body: 1.2±1.1 vs. 3.6±0.8; OR=0.91 (95% CI: 0.79 to 1.30); p=0.041 Visceral: 1.9±1.2 vs. 3.1±1.1; OR=0.72 (95% CI: 0.63 to 0.99); p=0.024 Nerve: 2.7±1.9 vs. 4.8±1.6; OR=0.90 (95% CI: 0.89 to 1.14); p=0.045 Favors CPGT intervention	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Very low
Quality of life	1 prospective cohort study (Chen et al. 2014[3])	Clinical Pharmacist-led Guidance Team-managed opioid therapy vs. control (543 patients)	Quality of Life (60-point scale; CPGT vs. Control): 48.3±11.3 vs. 37.6±9.4; OR=1.21 (95% CI: 0.75 to 1.58); p=0.032 Favors CPGT intervention	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Very low

[a] Methodological Quality takes into account the overall risk of bias rating of all the studies included in the evidence base;
[b] Inconsistency of results considers if the studies demonstrated similar positive or negative results (an inconsistent rating would indicate that the findings across studies were mixed);
[c] Indirectness of evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence) as well as the applicability of the study population; and
[d] Imprecision estimates the degree of uncertainty (based on variance or sample size) around an outcome's effect size.

AE: adverse event; CI: confidence interval; CPGT: clinical pharmacist-guidance team; OR:odds ratio; OTA: opioid treatment agreements; SNRI: serotonin-norepinephrine reuptake inhibitors; SR: systematic review; SUD: substance use disorder

Appendix A. Evidence Tables

Table 2. Systematic Review/Meta-analysis

Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results
Reference: Starrels et al. 2010[1] **Country:** USA **Purpose:** Systematic review to evaluate the risk mitigation efficacy of opioid treatment agreements (OTA) and routine urine drug testing (UDT) **Quality Rating:** Fair The review authors rated studies as Poor to Fair due to observational study designs, potential sampling bias or use of historical control groups, and the incongruence between complex management strategies offered at included studies' facilities and less comprehensive management options available for the majority of patients	MEDLINE, PsycINFO, EMBASE, and the Cochrane Central Register of Controlled Trials were searched through June 2009. The evidence base consisted of 5 prospective cohort studies and 6 retrospective cohort studies evaluating opioid misuse outcomes following OTA, routine UDT, or both risk mitigation strategies for treating chronic non-cancer pain **Inclusion Criteria:** Eligible studies needed to enroll 50 or more outpatients who were prescribed opioids for at least 3 months or who received opioid treatment described as "long-term" or "chronic." Studies evaluating OTA had to describe a written document that used any of 3 terms for the medication (opioid, controlled substance, or pain medication) and any of 4 terms for the type of document (agreement, contract, treatment plan, or informed consent). Studies evaluating UDT needed to employ routine testing routinely as part of a management strategy, rather than a single test to detect misuse for research purposes. UDT also needed to assess for controlled substances. **Exclusion Criteria:** Review authors excluded studies conducted in emergency departments, as well as studies of patients with cancer-related, acute, or postoperative pain.	**Number of Patients:** Enrollment ranged from 81 to 500 outpatients (total n=2,655 across 11 studies, with 2 studies reporting data from a single 500-patient pool) **Diagnosis:** Chronic non-cancer pain **Age:** All studies enrolled adult patients; across studies reporting detailed demographic data, the majority of patients were aged 40 to 65 **Gender:** % Female ranged from 4% to 59% **Intervention/Comparators:** OTA vs. control (2 studies) OTA and routine UDT vs. historical control (2 studies) OTA and UDT vs. no comparator (2 studies) OTA and routine UDT with monthly visits vs. no comparator (2 studies) OTA with monthly visits vs. no comparator (2 studies) Routine UDT vs. no comparator (1 study) **Follow-up:** Across included studies, follow-up periods ranged from 3 months to 4 years (2 studies did not report follow-up periods)	**Absolute Risk Reduction (ARR):** ARR >0% indicates that risk mitigation strategy is more effective than control for reducing opioid misuse OTA vs. Control: ARR=20.9% to 22.9%; maximum 95% CI: 10.6% to 31.2% (2 studies; n=426) OTA and routine UDT vs. historical control: ARR=6.5% to 8.6%; maximum 95% CI: 1.3% to 12.8% (2 studies; n=500) **Favors OTA and combination of OTA and routine UDT for reducing overall opioid misuse**

ARR: absolute risk reduction; CI: confidence interval; OTA: opioid treatment agreements; UDT: urine drug testing

Table 3. Individual Studies

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Reference: Im et al. 2015[2] **Country:** USA **Study Design:** Retrospective database study **Purpose:** To examine associations between the receipt of guideline-recommended care for opioid therapy and risk of suicide attempt. **Quality Rating:** Fair Very large population included; multiple relevant variables included in analysis, but a few relevant potential confounders not included.	**Number of Patients:** 487,462 veterans **Diagnosis:** Not reported; 80.8% received chronic short-acting (CSA) opioids, 19.2% received long-acting (LA) opioids **Age (Years):** Adults aged 18 years and older, mean and range not reported **Gender:** 6.5% female **Inclusion Criteria:** All veteran patients prescribed any short-acting opioids on a chronic basis (chronic short-acting) or any long-acting opioids from the VHA during fiscal year 2010 (FY10) were included in this analysis. Chronic use of short-acting opioids was defined as having at least 90 days of supply in FY10. **Exclusion Criteria:** Not reported	Multivariate, mixed-effects logistic regression analyses were conducted to define the associations between the risk of suicide attempt and receipt of guideline-recommended care at the individual level and rates of use of recommended care at the facility level, while accounting for patient risk factors. Separate analyses were done for patients receiving CSA opioids and patients receiving LA opioids, respectively. Individual-level variables included age, gender, and marital status. Age was categorized into three groups: younger than 31 years old, 31–55 years old, and greater than 55 years old. Physical/mental health status was represented by indicator variables for medical frailty, drug/alcohol/mood disorder, and traumatic brain injury. Binary indicator variables were used to identify whether patients received guideline-recommended care. Facility-level guideline-recommended care delivery rates were also used in the analysis. These rates were calculated for each VHA facility by dividing the number of patients on opioid therapy receiving each guideline recommended service by the total number of patients on opioid therapy within the VHA facility. **Follow-up:** 1 year	**CSA Opioid Therapy: Multivariate Logistic Regression Analysis** At the facility-level, patients prescribed CSA opioid therapy within VHA facilities ordering more drug screens were associated with decreased risk of suicide attempt (OR=0.2, 95% CI: 0.1 to 0.3). SUD subgroup: At the facility-level, SUD-diagnosed patients on CSA opioid therapy within VHA facilities ordering regular drug screens (defined as at least one drug screen for every 90 days of opioid supply) more consistently or providing more SUD specialty treatment/SUD specific pharmacotherapies were associated with decreased risk of suicide attempt (OR=0.3, 95% CI: 0.2 to 0.6). **LA Opioid Therapy: Multivariate Logistic Regression Analysis** At the facility level, the LA opioid therapy group within VHA facilities ordering more drug screens was associated with decreased risk of suicide attempt (OR=0.3, 95% CI: 0.2 to 0.6); in addition, the LA opioid therapy group within VHA facilities providing more follow-up after new prescriptions was associated with decreased risk of suicide attempt (OR=0.2, 95% CI: 0.0 to 0.7), and the LA opioid therapy group within VHA facilities having higher sedative co-prescription rates was associated with increased risk of suicide attempt (OR=20.3, 95% CI: 1.1 to 382.2). SUD subgroup: At the facility-level, SUD-diagnosed group on LA opioid therapy within VHA facilities providing more rehabilitation medicine were associated with decreased risk of suicide attempt (OR=0.3, 95% CI: 0.1 to 0.9), while SUD diagnosed patients within VHA facilities having higher sedative co-prescription rates and providing more SNRIs were associated with increased risk of suicide attempt

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			(OR=30.2 and 62.2; 95% CI: 1.1 to 829.3 and 2.2 to 1,769.3, respectively). **Comparisons associate increased adherence to guideline-recommended services with reduced risk of attempted suicide, and decreased guideline adherence with increased risk of attempted suicide**
Reference: Chen et al. 2014[3] **Country:** China **Study Design:** prospective, multicenter, double-arm, controlled cohort study **Purpose:** effectiveness and risk mitigation of chronic opioid therapy among cancer patients receiving interventions from Clinical Pharmacist-led Guidance Teams (CPGT) compared to patients in a control group **Quality Rating:** Poor Evaluation indicates that this study's quality rating is poor, primarily due to a lack of patient randomization and blinding. Study authors also acknowledge that patient data was collected using both in-person and phone methods, creating a potential source of data recording error and bias. The scale employed for quality of life assessments is also not widely validated or utilized.	**Number of Patients:** 542 cancer patients (269 in CPGT intervention group; 273 in control group) **Diagnosis:** Cancer pain, as diagnosed by an oncologist **Age (Years):** ≥18 years, mean and range not reported **Gender:** Male and female, percentages not reported **Inclusion Criteria:** Consenting inpatients who were able to receive opioid treatment for more than two weeks **Exclusion Criteria:** Patients with pain caused by acute cancerous symptoms or surgery, persistent nausea, vomiting and/or constipation, and a score of three or four according to Eastern Cooperative Oncology Group criteria	All patients received chronic opioid therapy managed by 1 of 2 protocols: **Clinical Pharmacist-led Guidance Teams (CPGT)**: Patients received opioid therapy managed by teams providing pain consultation, opioid monitoring, clinician and patient education, and patient follow-up **Control:** Patients and clinicians received opioid therapy with no CPGT support Study authors did not report specific opioid formulations or dosages prescribed to individual patients or study groups **Follow-up:** 6 months	**Pain Management (Numeric Pain Scale; CPGT vs. Control):** Lower values represent less patient-reported pain and better pain management **Bone:** 3.1±0.9 vs. 4.2±1.3; OR=0.86 (95% CI: 0.61 to 1.32); p=0.038 **Body:** 1.2±1.1 vs. 3.6±0.8; OR=0.91 (95% CI: 0.79 to 1.30); p=0.041 **Visceral:** 1.9±1.2 vs. 3.1±1.1; OR=0.72 (95% CI=0.63 to 0.99); p=0.024 **Nerve:** 2.7±1.9 vs. 4.8±1.6; OR=0.90 (95% CI: 0.89 to 1.14); p=0.045 **Favors CPGT intervention** **Quality of Life (60-point QLICP-GM scale; CPGT vs. Control):** Higher values represent better patient-reported quality of life 48.3±11.3 vs. 37.6±9.4; OR=1.21 (95% CI: 0.75 to 1.58); p=0.032 **Favors CPGT intervention** **AEs (CPGT vs. Control):** % represents observed rate of AEs, by category **Constipation:** 42.1% vs. 51.4%; OR=0.73 (95% CI: 0.61 to 0.93); p=0.041 **Nausea:** 15.1% vs. 22.8%; OR=0.62 (95% CI: 0.32 to 0.99); p=0.028 **Vomiting:** 15.7% vs. 22.1%; OR=0.58 (95% CI: 0.41 to 0.89); p=0.035

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			Delirium: 7.3% vs. 11.2%; OR=0.78 (95% CI: 0.56 to 0.98); p=0.088 **Excessive sedation:** 4.1% vs. 6.7%; OR=0.65 (95% CI: 0.47 to 0.78); p=0.062 **Itchy skin:** 13.4% vs. 12.4%; OR=1.05 (95% CI: 0.87 to 1.26); p=0.289 **Addiction:** 0% vs. 1.8% **All AEs favor CPGT intervention**

AEs: adverse events; CI: confidence interval; CSA: chronic short-acting opioids; CPGT: clinical pharmacist-led guidance teams; LA: long-acting opioids; OR: odds ratio; QLICP-GM: general module of the system of quality of life instruments for cancer patients; SNRI: serotonin-norepinephrine reuptake inhibitors; SUD: substance use disorder; VHA: Veterans Health Administration

Appendix B. References

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Appendix C. Excluded Studies

Table 4. Excluded Studies

Reference	Reason for Exclusion
Howlett et al. 2016[4]	Systematic review has no extractable data of interest for KQ7
Agarin et al. 2015[5]	Systematic review has no extractable data of interest for KQ7
Chou et al. 2015[6]	Systematic review has no extractable data of interest for KQ7; review authors specifically noted that "No [evaluated] study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse."
Argoff et al. 2014[7]	Systematic review has no extractable data of interest for KQ7
Dupouy et al. 2014[8]	Systematic review does not address patients with chronic pain, so outcomes are not relevant to KQ7
Provenzano and Viscusi 2014[9]	Systematic review has no extractable data of interest for KQ7
Bujold et al. 2012[10]	Does not address outcomes of interest for KQ7
Brown et al. 2011[11]	Does not address outcomes of interest for KQ7
Naylor et al. 2010[12]	Study does not address patients receiving chronic opioid therapy, so outcomes are not relevant to KQ7

Key Question 8: What is the safety and effectiveness of treatment of OUD (diagnosed or suspected) in patients with chronic pain? a.)Do outcomes vary by severity of OUD?

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Key Question 8: What is the safety and effectiveness of treatment of OUD (diagnosed or suspected) in patients with chronic pain? a.) Do outcomes vary by severity of OUD?

Summary of Evidence Base

- Our searches identified one systematic review and two additional RCTs that addressed this question.
    - The systematic review includes 14 studies, 12 of which reported results relevant to the key question.[1]
        - Review authors' analysis concluded that, among treated OUD patients, there was no effect of chronic pain on subsequent illicit opioid consumption
        - Meta-analysis of two studies (n=637) determined that comorbid chronic pain may have protective properties against illicit substance use
        - Review authors judged the strength of their evidence as poor, mainly due to the inclusion of several cross-sectional studies in comparison to few RCTs, and the inconsistency of treatment types, enrollment protocols, measurement tools, and assessed outcomes. (Quality of evidence ratings for outcomes reported in this systematic review: Low to Very low)
    - One RCT investigated the treatment efficacy of brief buprenorphine-naloxone therapy along with either standard medical management or a combination of standard medical management (SMM) and individual opioid dependence counseling (ODC).[2]
        - Study authors reported no association between chronic pain and treatment outcome for either study arm; similar results were reported for a subgroup of patients considered "adequately adherent" to treatments (Quality of evidence rating: Very low)
    - One RCT investigated the efficacy of adding structured cognitive behavioral therapy, motivational counseling, and urine drug testing protocols to close monitoring to improve high-risk patients' opioid use outcomes.[3]
        - Study authors report comparative data favoring adding structured cognitive behavioral therapy to reduce rates of opioid misuse among high-risk patients', even in the absence of improvements in patients' perceived pain. (Quality of evidence rating: Low to Very low)
- Our searches did not identify any systematic reviews or large, well-designed studies that comprehensively addressed this question, potentially due to the breadth of relevant therapeutic approaches, assessment methods, and outcomes of interest currently accepted by clinicians and researchers. Concurrently, the overall quality of the identified evidence base and associated evidence assessments is Low to Very Low, as a result of issues including high risk bias and significant methodological issues. Across identified studies, we also noted significant heterogeneity in study designs and enrollments, and assessed treatments and outcomes, complicating efforts to extract broader conclusions.

Overview of Evidence Base

Our searches identified one systematic review (SR) and two additional RCTs that addressed this question. The systematic review included 14 studies (10 cross-sectional studies, 3 cohort studies, and 1 RCT).[1] These studies evaluated the efficacy of multiple pharmacotherapies of interest, including varying doses and combinations of buprenorphine, levoacetomethadol (LAAM), methadone, and Suboxone® (buprenorphine-naloxone).[1] The two additional RCTs offer additional evidence regarding the efficacy of Suboxone combined with medical management and opioid dependence counseling and the utility of structured cognitive behavior therapy and compliance monitoring for improving opioid use outcomes among patients with chronic pain and comorbid OUD.[2,3] Excluded studies and the reasons for exclusion appear in Table 4, Appendix C.

Study Quality Rating

The studies included in the SR were rated as Poor quality by the authors of the review.[1] The primary methodological concerns were due to inclusion of several studies with cross-sectional study designs, along with issues regarding sample size calculations, outcome assessment blinding, and missing data management. Significant heterogeneity also existed across included studies' definitions of chronic pain and illicit opioid use behavior, measurement methodologies, and treatments of interest.

We assessed the quality (methodological risk of bias) of individual studies using criteria developed by the U.S. Preventive Services Task Force (USPSTF). The RCT by Weiss et al.,[2] reporting opioid abuse outcomes following the second phase of a two-phase study, was rated as Poor due to a lack of intent-to-treat analysis and significant patient attrition between trial phases, compromising data collection and introducing bias. In contrast, the RCT by Jamison et al.[3] was rated as Fair, as it incorporated dual controls groups and an intent-to-treat analysis. However, the study also had relatively low patient enrollment and a short follow-up time, limiting the authors' ability to conduct multivariate analyses or adequately probe for long-term effects of factors such as prior opioid abuse history on patient outcomes.[3] Further, the authors also acknowledge limitations in the number and types of interviews and assessment scales utilized in the study design.[3]

Overview of Study, Patient, and Intervention Characteristics

The systematic review by Dennis et al.[1] evaluated 14 studies, enrolling 3,540 patients. Of these studies, 13 enrolled adult patients, aged 20 to 54 years, with diagnosed OUD; one study enrolled adolescents and young adults aged 15 to 21 years. Across trials the percentage of enrolled female patients ranged from 24.1% to 46.3%. Six of these studies examined the efficacy of high-dose methadone (≥60 mg/day) for treating OUD comorbid to chronic pain, and two studies examined high-dose Suboxone (a combination of naloxone and at least 16 mg/day buprenorphine) for the same patient population. The remaining six studies each investigated a different comparison: low-dose Suboxone (combination of naloxone and less than 16 mg/day buprenorphine); low-dose buprenorphine (<16 mg/day) vs. high-dose buprenorphine (≥16 mg/day); low-dose methadone (<60 mg/day) vs. high-dose methadone (≥60 mg/day); low-dose methadone vs. low-dose buprenorphine; low-dose methadone vs. low-dose Suboxone; and high-dose methadone vs. low-dose methadone vs. low-dose LAAM (<85 mg/day) vs. high-dose LAAM (≥85 mg/day). Minimum treatment duration was 12 weeks, and outcomes were assessed at times between 12 weeks and 18 months from treatment initiation.

Weiss et al.[2] enrolled 360 patients, of whom 138 reported chronic pain at the start of the trial period; 41.9% of patients were female. The study explored the efficacy of adding either standard medical management or standard medical management and opioid drug counseling to Suboxone therapy for treating OUD over 12 weeks.

The RCT by Jamison et al.[3] enrolled 62 patients, aged 24 to 63 years; 43.5% of patients were female. The study's authors assessed the efficacy of a structured cognitive behavior therapy program and dedicated compliance monitoring (including urine drug testing, compliance checklists, and individual and group counseling sessions) on opioid misuse over a 6-month treatment period.

Outcomes and Synthesis of Results

Pharmacotherapy Interventions

Dennis et al.'s[1] systematic review included 14 studies that, in total, evaluated the treatment efficacy of various doses and combinations of 4 drugs — buprenorphine, LAAM, methadone, and Suboxone — among patients with OUD and comorbid chronic pain. The review authors found no evidence of interactions between chronic pain and buprenorphine, methadone, or Suboxone therapies' impact on patients' illicit substance use (Prevalence OR: 0.57; 95% CI: 0.41 to 0.79). A single study[4] reported that chronic pain increased patient's risk for illicit opioid use among patients administered LAAM, but had no influence on illicit non-opioid substance use. Review authors did not include this study in any meta-analyses, primarily due to significant cross-study differences in defining illicit substance use behavior.

The sole RCT[5] included in the Dennis et al review investigated the comparative treatment efficacy of low-dose methadone and low-dose Suboxone in patients with OUD and comorbid chronic pain. Using self-reported opioid use measures from these patients, the original study authors report that methadone was more effective than Suboxone for reducing opioid misuse (misuse rate: 0% versus 38.5%; p=0.039). The authors found no significant difference in pain relief efficacy between these two therapies.[5]

Combined Behavior Therapy and Pharmacotherapy or Non-pharmacotherapy Risk Mitigation and Pharmacotherapy Interventions

Weiss et al.[2] conducted an RCT comparing the effects of chronic pain on patients receiving Suboxone therapy with standard medical management protocols and patients receiving Suboxone therapy combined with standard medical management protocols and individual opioid dependence counseling. Study authors reported no effect of chronic pain on treatment outcomes (OR=1.3; 95% CI: 0.8 to 2.0; p=0.240). Additionally, the authors noted a similar lack of effect of chronic pain among an enrolled subpopulation of "adequately adhering" patients (OR=0.5; 95% CI: 0.2 to 1.5; p=0.213). Study authors reported similar findings among patients at 18 months post-treatment (OR=0.43; 95% CI: 0.16 to 1.17; p>0.05).[1]

Jamison et al. 2010[3] reported results from an RCT investigating the effectiveness of close monitoring and cognitive behavioral therapy on illicit substance use among high-risk patients with OUD and comorbid chronic pain. The authors report that, compared to a matched high-risk group receiving standard care, patients receiving additional monitoring and cognitive behavior therapy exhibited significantly reduced illicit substance use over 6 months (Percentage of patients with positive Drug Misuse Index [DMI] scores: 73.7% versus 26.3% versus 25.0%; Chi^2=12.16, p<0.01). Additionally, the authors used patient self-reporting to examine between-group differences in pain levels and the degree to which pain interfered with

patients' daily activities; these measures may indirectly reflect differences in treatment-related pain relief and quality of life, respectively. Authors reported a group difference in worst perceived pain, least perceived pain, and average perceived pain favoring the high-risk group receiving additional monitoring and behavior therapy; however, analysis of activity interference reporting reflected no significant difference between study groups. (See Table 3, below)

Overall Quality of Evidence Rating

The overall quality of evidence ratings ranged from Very low to Low across different outcomes. Low ratings reflected the limitations of Fair- to Poor-quality studies, while Very Low ratings additionally reflected additional serious or imprecision or indirectness in the treatment effect estimate. Very low quality evidence supported the relationship between pain and illicit opioid use.[1] Very low quality evidence supported the comparative pain relief and drug misuse reduction efficacies of various OUD pharmacotherapies.[1] Low quality evidence supported the relationship between pain and illicit non-opioid use in patients with chronic pain who were receiving substitute opioid therapy for OUD.[1] Very low quality evidence supported the use of concomitant individualized opioid dependence counseling in patients with chronic pain and OUD who were maintained on Suboxone and medical management.[2] Finally, Very low quality evidence supported the effectiveness of close monitoring and cognitive behavioral therapy on illicit substance use among high-risk patients with OUD and comorbid chronic pain for the outcomes of illicit substance use, pain levels, and quality of life.[3]

Table 1. Overall Assessment of Quality of Evidence Base

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Methadone								
Effect of pain on illicit opioid use	1 SR (Dennis et al. 2015[1])	High-dose methadone (≥60 mg/day) (2 cross-sectional studies with 405 patients)	Prevalence OR=0.70, 95% CI: 0.41 to 1.17 No significant effect of chronic pain on illicit opioid use behaviors	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (95% CI includes possibility that chronic pain reduces illicit opioid use)	Very low
Effect of pain on illicit non-opioid substance use	1 SR (Dennis et al. 2015[1])	High-dose methadone (≥60 mg/day) (2 cross-sectional studies with 637 patients)	Prevalence OR: 0.57; 95% CI: 0.41 to 0.79 Favors chronic pain for reducing illicit non-opioid substance use; patients are 43% less likely to abuse substances if they have comorbid chronic pain and OUD	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Methadone Versus Suboxone								
Effect of pain on illicit opioid use	1 SR (Dennis et al. 2015[1])	Low-dose methadone (<60 mg/day) vs. low-dose Suboxone (<16 mg/day buprenorphine + naloxone) (1 study with 54 patients)	OR: 0.280, 95% CI: 0.042 to 1.878, p=0.371 No significant effect of chronic pain on illicit opioid use	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (95% CI includes possibility of an effect in either direction)	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Pain relief	1 SR (Dennis et al. 2015[1])	Low-dose methadone (<60 mg/day) vs. low-dose Suboxone (<16 mg/day buprenorphine + naloxone) (1 study with 54 patients)	Percent change of pain from baseline (mean±SD; buprenorphine/naloxone vs. methadone) 87.4±33.4 vs. 88.6±24.5; p=0.918 No significant difference between treatment groups	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very low
Drug misuse	1 SR (Dennis et al. 2015[1])	Low-dose methadone (<60 mg/day) vs. low-dose Suboxone (<16 mg/day buprenorphine + naloxone) (1 study with 54 patients)	Self-reported substance abuse rates (percentage of patients; buprenorphine/ naloxone vs. methadone) Positive urine for opioids: 38.5 vs. 15.4; OR=0.280 (95% CI: 0.042 to 1.878); p=0.371 Positive urine for cocaine: 15.4 vs. 0; p=0.478 Positive urine for other drugs: 38.5 vs. 38.5; OR=1.000 (95% CI: 0.197 to 5.068); p=1.000 Self-reported opioid use: 38.5 vs. 0; p=0.039 Self-reported alcohol use: 30.8 vs. 15.4; OR=0.409 (95% CI: 0.060 to 2.769); p=0.645 Self-reported use of other drugs: 38.5 vs. 23.1; OR=0.480 (95% CI: 0.087 to 2.645); p=0.673 Difference in self-reported opioid use favors	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
			methadone treatment; no other significant differences were found between groups across other analyses					
Suboxone and Medical Management Versus Suboxone and Medical Management and Opioid Dependence Counseling								
Effect of pain on illicit opioid use	1 RCT (Weiss et al. 2014[2])	Suboxone and medical management vs. Suboxone and medical management and individual opioid dependence counseling (360 patients)	Main effect interaction: chronic pain x treatment condition (12 week follow-up) OR=1.3; 95% CI: 0.8 to 2.0; p=0.240 Secondary interaction: chronic pain x phase 2 treatment group (12 week follow-up) OR=0.6; 95% CI: 0.2 to 1.4; p=0.218 No significant association between chronic pain and treatment outcome	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (95% CIs too wide to rule out a possible association)	Very low
Effect of pain on illicit opioid use	1 SR (Dennis et al. 2015[1])	Suboxone and medical management vs. Suboxone and medical management and individual opioid dependence counseling (252 patients	Main effect interaction: chronic pain x treatment condition (18 month follow-up) OR=0.43; 95% CI: 0.16 to 1.17; p>0.05 No significant association between chronic pain and treatment outcome	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (95% CIs too wide to rule out a possible association)	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Close Monitoring and Cognitive Behavior Therapy Protocol Versus Standard of Care								
Drug misuse	1 RCT (Jamison et al. 2010[3])	Close monitoring with regular drug testing and cognitive behavior therapy vs. standard care (regular physician visits and reporting) (62 patients)	Drug Misuse Index (High-risk control vs. high-risk experimental vs. low-risk control): 73.7% vs. 26.3% vs. 25.0%; X^2=12.16, p<0.01 Comparison favors experimental intervention for reducing opioid misuse among high-risk patients, with no significant difference observed between high-risk experimental and low-risk control groups	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (Single small study)	Low
Quality of Life	1 RCT (Jamison et al. 2010[3])	Close monitoring with regular drug testing and cognitive behavior therapy vs. standard care (regular physician visits and reporting) (62 patients)	Electronic diary activity interference ratings (100 point scale) (High-risk control vs. high-risk experimental vs. low-risk control): AI, Daily routine: 67.00±28.66 vs. 63.73±26.02 vs. 59.03±20.75; F=3.18, p<0.05 AI, Social: 63.20±31.29 vs. 63.10±28.69 vs. 54.15±24.00; F=4.20, p<0.05 AI, Sex: 54.14±37.11 vs. 61.77±36.94 vs. 59.90±30.19; NS	Serious limitations (-1)	No serious inconsistency	Serious indirectness (-1)[1]	Serious imprecision (-1) (Single small study)	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
			AI, Sleep: 64.74±28.84 vs. 65.79±27.26 vs. 62.64±26.38; NS AI, Work: 79.48±27.71 vs. 71.30±30.45 vs. 69.21±26.06; F=4.89, p<0.05 AI, Outdoor/recreation: 73.58±29.12 vs. 73.90±24.62 vs. 66.53±22.61; F=3.24, p<0.05 AI, Appetite: 51.81±31.34 vs. 50.27±30.30 vs. 40.33±24.68; F=5.80, p<0.01 No significant difference between high-risk groups' perceptions of how pain interfered with daily activities					
Pain relief	1 RCT (Jamison et al. 2010[3])	Close monitoring with regular drug testing and cognitive behavior therapy vs. standard care (regular physician visits and reporting) (62 patients)	Electronic diary perceived pain ratings (100 point scale) (High-risk control vs. high-risk experimental vs. low-risk control): Worst pain: 76.06±18.58 vs. 76.87±17.25 vs. 67.53±22.03; F=8.54, p<0.001 Least pain: 53.44±24.31 vs. 46.62±23.84 vs. 42.43±21.21; F=7.35; p<0.001	Serious limitations (-1)	No serious inconsistency	Serious indirectness (-1)[1]	Serious imprecision (-1)	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
			Average pain: 65.32±20.80 vs. 57.45±20.42 vs. 56.06±20.49; F=7.56, p<0.001 No significant difference between high-risk groups' worst perceived pain, while least perceived pain and average perceived pain measures favor high-risk experimental group.					

[a] Methodological Quality takes into account the overall risk of bias rating of all the studies included in the evidence base;
[b] Inconsistency of results considers if the studies demonstrated similar positive or negative results (an inconsistent rating would indicate that the findings across studies were mixed);
[c] Indirectness of evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence) as well as the applicability of the study population; and
[d] Imprecision estimates the degree of uncertainty (based on variance or sample size) around an outcome's effect size.
[1] Indirectness related to use of patient self-reports to examine between-group differences in pain levels and the degree to which pain interfered with patients' daily activities
AI: activity interference; CI: confidence interval; mg: milligram; OR: odds ratio; OUD: opioid use disorder; RCT: randomized controlled trial; SR: systematic review

Appendix A. Evidence Tables

Table 2. Systematic Review/Meta-analysis

Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results
Reference: Dennis et al. 2015[1] **Country:** USA **Purpose:** Systematic review and meta-analysis evaluating the effect of comorbid chronic non-cancer pain on treatment outcomes among patients with OUD **Quality Rating:** Poor The quality of evidence included in this review is poor, primarily due to reliance on several studies with cross-sectional study designs, along with issues regarding sample size calculations, outcome assessment blinding, and missing data management. Significant heterogeneity also exists across included studies' definitions of chronic pain and illicit opioid use behavior, measurement methodologies, and treatments of interest.	Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Database of Systematic Reviews, ProQuest Dissertations and theses Database, Cochrane Central Register of Controlled Trials, World Health Organization International Clinical Trials Registry Platform Search Portal, and National Institutes for Health Clinical Trials Registry databases were searched. The evidence base consisted of 10 cross-sectional studies, 3 cohort studies, and 1 randomized controlled trial evaluating the effect of comorbid chronic pain on treatment outcomes for patients with OUD. **Inclusion Criteria:** Eligible studies were required to assess the impact of pain on any of the following treatment outcomes: physical, psychological, or social outcomes for patients receiving opioid agonist or antagonist substitution therapy for opioid use disorder. Study participants were required to be on a maintenance therapy for the opioid use disorder. **Exclusion Criteria:** Review authors excluded studies evaluating patients administered opioid use therapies for treating pain, rather than OUD.	**Number of Patients:** Enrollment ranged from 54 to 489 outpatients (total n=3,128 across 14 studies) **Diagnosis:** Chronic non-cancer pain **Age:** 13 of 14 studies enrolled adults aged 20 to 54 years; 1 study enrolled adolescents and young adults aged 15 to 21 years **Gender:** % Female ranged from 24.1% to 46.3% across studies reporting detailed demographic data **Intervention/Comparators:** High-dose methadone: 6 studies Low-dose Suboxone: 1 study; Suboxone administered in formulations containing ≤16 mg/day buprenorphine plus naloxone High-dose Suboxone: 2 studies; Suboxone administered in formulations containing ≥16 mg/day buprenorphine plus naloxone Low-dose buprenorphine vs. high-dose buprenorphine: 1 study Low-dose methadone vs. high-dose methadone: 1 study Low-dose methadone vs. low-dose buprenorphine: 1 study Low-dose methadone vs. low-dose Suboxone: 1 study High-dose methadone vs. low-dose methadone vs. high-dose LAAM vs. low-dose LAAM: 1 study	**Effect of Pain on Illicit Opioid Consumption:** Patients were considered as having illicitly consumed opioids if ≥1 positive urine tests during a designated time period Prevalence OR=0.70, 95%CI: 0.41 to 1.17 (2 studies investigating methadone therapy; n=405) **Meta-analysis Indicates No Effect of Pain on Illicit Opioid Consumption** Systematic review authors determined that 12 of 14 studies evaluated the impact of chronic pain on illicit opioid consumption; of these 12, the remaining 10, including 1 RCT (OR: 0.280, 95% CI: 0.042 to 1.878, p=0.371) demonstrated no significant effect. **Effect of Pain on Illicit Non-opioid Substance Consumption:** Patients were considered as having illicitly consumed opioids if ≥1 positive urine tests during a designated time period Prevalence OR: 0.57; 95% CI: 0.41 to 0.79 (2 studies investigating methadone therapy; n=637) **Meta-analysis Indicates that Pain is Protective Against Illicit Non-opioid Substance Use; Odds of Non-opioid Illicit Substance Use are Reduced by 43% in Participants with Comorbid Pain:** Systematic review authors determined that 7 of 14 studies evaluated the impact of chronic pain on illicit non-opioid substance consumption; 5 studies were excluded from this meta-analysis as they did

Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results
		Low-dose buprenorphine: oral buprenorphine administered at <16 mg/day High-dose buprenorphine: oral buprenorphine administered at ≥16 mg/day Low-dose LAAM: oral LAAM administered at <85 mg/day High-dose LAAM: oral LAAM administered at ≥85 mg/day Low-dose methadone: oral methadone administered at <60 mg/day High-dose methadone: oral methadone administered at ≥60 mg/day Low-dose Suboxone: oral Suboxone formulations containing <16 mg/day buprenorphine plus naloxone High-dose Suboxone: oral Suboxone formulations containing ≥16 mg/day buprenorphine plus naloxone **Follow-up:** Across included studies, follow-up periods ranged from 12 weeks to 18 months	not measure substance use as the percentage of participants that reported illicit substance use. **Pain Relief Efficacy:** Percent change of pain from baseline (mean±SD; buprenorphine/naloxone vs. methadone, n=54) 87.4±33.4 vs. 88.6±24.5; p=0.918 **No Significant Difference Between Treatment Groups** No other included studies reported comparative pain relief data

CI: confidence interval; LAAM: levoacetylmethadol (levo-α-acetylmethadol); OR: odds ratio; OUD: opioid use disorder

Table 3. Individual Studies

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Reference: Weiss et al. 2014[2] **Country:** USA **Study Design:** 2-phase randomized controlled trial **Purpose:** Secondary analysis investigating efficacy of individual drug counseling and standard medical management for improving opioid use outcomes **Quality Rating:** Poor Evaluating this study for this key question, the quality rating is poor due to a lack of intent-to-treat analysis and significant patient attrition between trial phases.	**Number of Patients:** 360 total patients; 138 (38.3%) reported current chronic pain at intake for study phase 2. **Diagnosis:** Current opioid dependence; patients invited to participate in study phase 2 experienced an opioid relapse following study phase 1. **Age (Years):** 18 years and older **Gender:** 41.9% female **Inclusion Criteria:** Psychologically stable treatment-seeking patients who met DSM-IV criteria for current opioid dependence **Exclusion Criteria:** Key exclusion criteria included a requirement of ongoing pain management with opioids, currently unstable psychiatric illness, pregnancy, or concurrent formal substance use disorder treatment other than mutual-help groups.	Study phase 1 consisted of a short buprenorphine-naloxone treatment protocol (2-week induction and stabilization, 2 week tapering period, and 8-week follow-up period). Patients enrolling in study phase 2 received 12 weeks' buprenorphine-naloxone treatment followed by a 4 week tapering period and 8-week follow-up period. In both phases, patients were randomized to 1 of 2 experimental arms: **SMM:** Patients received weekly standard medical management visits, including medication distribution and brief medically-oriented counseling. **SMM+ODC:** Patients received weekly standard medical management visits and longer opioid dependence counseling sessions, conducted twice-weekly for the initial 6 treatment weeks and weekly thereafter. The minimum and maximum medication doses were 8 mg and 32 mg daily, respectively. **Follow-up:** 12 weeks	A logistic regression model was created and adjusted for patients' phase 1 treatment condition. **Main Effect Interaction: Chronic Pain x Treatment Condition:** OR=1.3; 95% CI: 0.8 to 2.0; p=0.240 **Secondary Interaction: Chronic Pain x Phase 2 Treatment Group:** OR=0.6; 95% CI: 0.2 to 1.4; p=0.218 **No association between chronic pain and treatment outcome.** Study authors considered 266/360 patients to meet criteria for adequate treatment adherence **Secondary Interaction Among Adequately Adherent Patients: Chronic Pain x Phase 2 Treatment Group:** OR=0.5; 95% CI: 0.2 to 1.5; p=0.213 **No association between chronic pain and treatment outcome.**
Reference: Jamison et al 2010[3] **Country:** USA **Study Design:** Randomized controlled trial **Purpose:** Investigation of efficacy of close monitoring and cognitive behavior therapy protocol for increasing opioid therapy compliance among chronic pain patients meeting criteria for high risk of opioid misuse **Quality Rating:** Fair	**Number of Patients:** 62 (21 patients in each of two randomized high-risk groups; 20 patients in low-risk control group) **Diagnosis:** Chronic back or neck pain **Age (Years):** 24 to 63 years old (mean = 47.7 years old) **Gender:** 43.5% female **Inclusion Criteria:** Included patients who had chronic back or neck pain for at least 6 months' duration; averaged scores of 4 or greater on a pain intensity scale of 0–10 with medication; were prescribed opioid therapy	All patients completed baseline and end-of-study assessments, including PDUQ and UDT **High-Risk Control:** Patients completed monthly electronic diaries and received standard care, including monthly physician contact and visits to a university-based pain treatment center **High-Risk Experimental:** In addition to medical treatment identical to high-risk control patients, experimental patients participated in a structured cognitive behavioral training program,	58/62 patients were followed and completed post-treatment questionnaires **Drug Misuse Index (DMI; High-risk Control vs. High-risk Experimental vs. Low-risk Control):** DMI is based on patients' scores on the self-reported PDUQ, physician-reported ABC, and urine toxicology results; a positive PDUQ, or positive ABC and toxicology results, results in a positive DMI and correlates with increased opioid misuse. Percentage represents number of patients with positive DMIs, per study group

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Study incorporates dual control groups and intent-to-treat analysis, but had relatively low patient enrollment and a short follow-up time, limiting the authors' ability to conduct multivariate analyses or adequately probe for long-term effects of factors such as prior opioid abuse history on patient outcomes. The authors also acknowledge limitations in the number and types of interviews and assessment scales administered.	for pain for at least 6 months. Patients enrolled in high-risk study groups were considered to have high risk for opioid misuse, based on history of prescription opioid misuse or recent Screener for Opioid Abuse for Pain Patients scores greater than 18 **Exclusion Criteria:** Patients were excluded for any of the following: current diagnosis of cancer or any other malignant disease; current diagnosis of acute osteomyelitis or acute bone disease; past or present DSM-IV diagnosis of schizophrenia, delusional disorder, psychotic disorder, or dissociative disorder; current pregnancy; any clinically unstable systemic illness judged to interfere with treatment; acute condition requiring surgery; and any active addiction disorder	incorporating individual compliance sessions and monthly group motivational counseling sessions, substance misuse education worksheets, and monthly opioid compliance checklists and UDT. **Low-Risk Control:** Patients completed monthly electronic diaries and received standard care, including monthly physician contact and visits to a university-based pain treatment center Study authors did not report specific opioid formulations or dosages prescribed to individual patients or study groups **Follow-up:** 6 months	73.7% vs. 26.3% vs. 25.0%; Chi^2=12.16, p<0.01 **Comparison favors experimental intervention for reducing opioid misuse among high-risk patients, with no significant difference observed between high-risk experimental and low-risk control groups** **Electronic Diary Ratings (High-risk Control vs. High-risk Experimental vs. Low-risk Control):** Pain data is based on visual analog pain scales; activity interference is derived from patient self-reporting of the degree to which pain interfered with various daily activities during the past 24 hours. Scores for all measures were converted to 0-100 scales; higher scores reflect greater perceived pain or activity interference **Worst Pain:** 76.06±18.58 vs. 76.87±17.25 vs. 67.53±22.03; F=8.54, p<0.001 **Least Pain:** 53.44±24.31 vs. 46.62±23.84 vs. 42.43±21.21; F=7.35; p<0.001 **Average Pain:** 65.32±20.80 vs. 57.45±20.42 vs. 56.06±20.49; F=7.56, p<0.001 **No significant difference between high-risk groups' worst perceived pain, while least perceived pain and average perceived pain measures favor high-risk experimental group.** **AI, Daily Routine:** 67.00±28.66 vs. 63.73±26.02 vs. 59.03±20.75; F=3.18, p<0.05 **AI, Social:** 63.20±31.29 vs. 63.10±28.69 vs. 54.15±24.00; F=4.20, p<0.05 **AI, Sex:** 54.14±37.11 vs. 61.77±36.94 vs. 59.90±30.19; NS

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			AI, Sleep: 64.74±28.84 vs. 65.79±27.26 vs. 62.64±26.38; NS **AI, Work:** 79.48±27.71 vs. 71.30±30.45 vs. 69.21±26.06; F=4.89, p<0.05 **AI, Outdoor/recreation:** 73.58±29.12 vs. 73.90±24.62 vs. 66.53±22.61; F=3.24, p<0.05 **AI, Appetite:** 51.81±31.34 vs. 50.27±30.30 vs. 40.33±24.68; F=5.80, p<0.01 **No significant difference between high-risk groups' perceptions of how pain interfered with daily activities**

ABC: addiction behaviors checklist; AI: activity interference; CI: confidence interval; DMI: drug misuse index; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ODC: opioid dependence counseling; OR: odds ratio; PDUQ: prescription drug user questionnaire; SMM: standard medical management; UDT: urine drug testing

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Appendix C. Excluded Studies

Table 4. Excluded Studies

Reference	Reason for Exclusion
Eilender et al. 2015[6]	Not a systematic review or clinical trial of any design
Kowalczyk et al. 2015[7]	Study does not address patients with chronic pain, so outcomes are not relevant to KQ8
Potter et al. 2015[8]	Less than 45% of enrolled patients had chronic pain and comorbid opioid use disorder, and no subgroup analysis was conducted for this patient population
Stein et al. 2015[9]	Study excluded patients with chronic pain requiring chronic opioid therapy, so outcomes are not relevant to KQ8
Clark et al. 2014[10]	Systematic review does not include any RCTs
Larney et al. 2014[11]	Study does not address patients with chronic pain, so outcomes are not relevant to KQ8
Wachholz et al. 2014[12]	Study does not report outcomes of interest for KQ8
Neumann et al. 2013[5]	Study included in systematic review by Dennis et al.[1]
Saxon et al. 2013[13]	Study does not address patients with chronic pain, so outcomes are not relevant to KQ8
Tetrault et al. 2012[14]	Study does not address patients with chronic pain, so outcomes are not relevant to KQ8
Brunen et al. 2011[15]	Study does not address KQ8
Weiss et al. 2011[16]	Study excluded patients with chronic pain requiring chronic opioid therapy, so outcomes are not relevant to KQ8
Weiss et al. 2010[17]	Study does not report outcomes of interest for KQ8

Key Question 9: What is the safety and effectiveness of different tapering strategies and schedules?

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Key Question 9: What is the safety and effectiveness of different tapering strategies and schedules?

Summary of Evidence Base

Based on our searches and inclusion criteria for this report, we identified two studies that were included as evidence for this key question. The identified studies, described below, addressed the safety and effectiveness of different tapering strategies and schedules in patients suffering from chronic pain.

- Our searches identified two studies, a prospective longitudinal study (Wang et al. 2011[1]) and a randomized controlled trial (RCT; Nomura et al. 2011[2]) as evidence for this key question.
- Wang et al. 2011[1] focused on the changes in pain sensitivity during opioid tapering and withdrawal in chronic lower back pain (cLBP) patients on long-term opioid therapy. The findings suggested that long-term use of opioids did not reduce pain sensitivity. However, opioid tapering did induce brief hyperalgesia.
- Nomura et al. 2011[2] evaluated the safety and efficacy of conversion methods in chronic cancer pain patients. Overall, authors reported an excellent safety profile and sustained efficacy for the 6-h conversion method compared with the 12-h conversion method. This was performed in the form of continuous intravenous infusion conversion to transdermal fentanyl using a two-step tapering approach.
- Both studies[1,2] received a Very low quality rating for their outcomes due to serious study limitations and imprecision in their findings based on the GRADE criteria.

Overview of Evidence Base

Our searches of the literature identified one prospective longitudinal study and one RCT that considered the evidence for the safety and effectiveness of different tapering strategies and schedules in patients with chronic pain. The prospective longitudinal study by Wang et al. 2011[1] enrolling 98 patients, investigated pain sensitivity after tapering of long-term opioid use in a homogeneous cLBP patient population. Pain sensitivity was monitored for 6 months.[1] The double-blinded RCT by Nomura et al. 2011 evaluated 87 patients and compared the safety and efficacy of a 12-hour conversion method versus a 6-hour conversion method in chronic cancer pain management. Patients had follow-ups at 6, 12, 18, 24 and 48 hour intervals.[2] Studies excluded as evidence for this key question and reasons for their exclusion are presented in Table 4 of the Appendix.

Study Quality Rating

The Wang et al. 2011[1] longitudinal study was rated Fair as the authors used appropriate attention to confounders in analysis but had less than 80% follow-up at 6 months. Nomura et al. 2011[2] was rated Fair mostly due to lack of intent-to-treat analysis. The study however used adequate randomization and allocation concealment methods, and matching baseline characteristics based on USPSTF criteria.

Overview of Study, Patient, and Intervention Characteristics

Below we provide a brief description of the study, patient, and intervention characteristics of the studies that make up the evidence base for this key question. Additional information is provided in Table 2.

The Wang et al. 2011[1] study investigated the long-term (17 months) effects of opioid analgesics on pain sensitivity and evaluated the changes in pain sensitivity during opioid tapering and withdrawal in patients currently using opioids compared with two groups of non-opioid users. The patient population included mostly non-elderly (mean age 47.6 years) women (54.1%) diagnosed with chronic myofascial LBP. All patients were on active opioid therapy treatments, defined as intake of a morphine equivalent dose of at least 30 mg per day every day for more than 3 months. The authors used the quantitative sensory testing (QST) technique to assess pain sensitivity at 1 day before (T1), 3 weeks after (T2), and 6 months after the start of opioid tapering (T3) in 35 patients with both cLBP and opioid medication (OP). The comparison groups included 35 opioid-naïve (ON) cLBP patients who had not used opioids for 3 months prior to baseline, and 28 healthy controls (HC) with neither pain nor opioid intake. Tapering was performed by reducing the dosage of opioid preparation by half every 3 days until the patients became opioid clean. All patients had stopped the use of opioids by T2.

The other study was a double-blinded RCT (Nomura et al. 2011)[2] designed to compare the safety and efficacy of the conversion from continuous intravenous infusion to transdermal fentanyl using two-step tapering of the continuous intravenous infusion in the 12 h (12-h method) or in the 6 h (6-h method) conversion. The study included mostly elderly patients (mean age 60 years) who were diagnosed with chronic cancer pain. Majority of the patients were men (70.1%) with assessable pain intensity being pretreated with continuous intravenous fentanyl. The mean dosages of the applied fentanyl transdermal patch (post randomization) were 23.3±13.3 μg/h (range, 12.5 to 100 μg/h) in the 12-h group and 28.3±21.4 μg/h (range, 12.5 to 100 μg/h) in the 6-h group. Patients were randomly allocated to one of the conversion method groups. In the 12-h group, fentanyl was administered using the 12-h method, and saline was administered using the 6-h method. In the 6-h group, fentanyl was administered using the 6-h method, and saline was administered using the 12-h method. Pain intensity and bolus use frequency between the two treatment methods were assessed.

Outcomes and Synthesis of Results

Below we provide an overview of the main findings of each study. Additional information and results are provided in Table 2.

Tapering Intervention in Chronic Lower Back Pain Patients on COT

Pain sensitivity (heat pain thresholds): Significant differences were reported in one study (Wang et al. 2011[1]) among the three groups at all three time points (T1: p=0.001, T2: p=0.015, T3: p=0.008) but not between the two cLBP patient groups (i.e. opioid medication group and opioid naïve group). At T3 (6 months after start of tapering), the heat pain thresholds of cLBP and opioid medication patients still remained lower than healthy controls (p=0.017), while those of cLBP and opioid naïve patient group were normalized.

Pain sensitivity (cold pain thresholds): cLBP and opioid medication patients showed lower cold pain thresholds at T2 (at 3 weeks) than cLBP and opioid naive patients and healthy controls.[1]

Pain sensitivity (warm stimuli): One study reported that compared with T1 (1 day before start of tapering), cLBP and opioid medication patients reacted to warm stimuli significantly faster at T2 (at 3 weeks) (p=0.029), while cLBP and opioid naïve patients did not change their pain profile. At T3 (6 months after start of tapering), cLBP and opioid medication patients showed a further increase in speed of reaction to warm stimuli (p=0.01) and a further lowering of cold pain thresholds (p=0.026) relative to T2.[1]

Adverse events: Nausea, weakness, increased sweating, and sleep disturbance were reported during week 1.[1]

Statistically significant correlations were found between sensation of warmth in the hand and both age (r=0.308, p=0.015) and sex (r=0.271, p=0.003). Moderate correlations were observed with NRS scores and thermal sensation. No correlations were determined between QST values and depression, pain duration, opioid dose, or opioid duration.[1]

The authors concluded that long-term use of opioids did not reduce pain sensitivity in cLBP patients.

Tapering Conversion Intervention in Chronic Cancer Pain Patients

Pain intensity: No significant increases in pain intensity were found in both groups. In the 12-h group, significant decreases in pain intensity were identified at 6h and 12-h compared with that prior to application of the fentanyl patch (6-h 95% CI: 0.17 to 0.63; p=0.003; 12-h 95% CI: 0.23 to 0.84; p=0.003). There were no significant decreases in pain intensity in the 6-h group (p>0.05).[2]

Bolus use: No significant between group differences were reported.[2]

Adverse events/toxicity: A higher incidence of opioid-related adverse events above baseline was found in the 12-h conversion group compared with the 6-h conversion group (95% CI: 0.01 to 0.55; p=0.002). Similarly, significant differences in the incidence of adverse events was observed in the 12-h method group versus the 6-h method group (12-h group=25.6%, 6-h group=2.3%; 95% CI: 0.01 to 0.55; p=0.002). Adverse events, which were considered opioid-related, led to early discontinuations for 16% of patients in the 12-h method group. Grade 3 or more adverse events occurred in seven patients in the 12-h group (p=0.005).[2]

The authors reported an "excellent safety profile" and sustained efficacy for the 6-h conversion method.

Overall Quality of Evidence Rating

- Table 1 presents the overall quality ratings for outcomes reported in the studies included as evidence for this key question. The two studies included a prospective longitudinal analysis (Wang et al. 2011[1]) and a RCT (Nomura et al. 2011[2]). The evidence presented in Wang et al. 2011[1] received a Very low rating for the outcome of pain sensitivity due to very serious study limitations (non-RCT study design and less than 80% follow-up) and very serious imprecision related to both lack of precision in reporting statistical outcomes (only p values were reported) and the evidence base consisting of only one trial with small sample size. The evidence presented in Nomura et al. 2011[2] received a Very low rating for the outcomes of pain intensity, bolus use and adverse events due to very serious study limitations related to a lack of intent-to-treat analysis and serious imprecision related to the evidence base consisting of only one trial with small sample size.

Table 1. Overall Assessment of Quality of Evidence Base

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Tapering in cLBP Patients on Opioid Therapy								
Pain sensitivity (heat pain threshold)	Prospective longitudinal study (Wang et al. 2011[1])	Tapering was performed in patients with cLBP (with/without OT) and healthy controls with neither pain nor opioid therapy. (98 patients)	Significant differences in heat pain thresholds were found among the three groups at all three time points (T1: p=0.001, T2: p=0.015, T3: p=0.008), but not between the two patient groups.	Very serious study limitations (-2)	No serious inconsistency	No serious indirectness	Very serious imprecision (-2) (One single small study, imprecise description of statistical outcomes)	Very low
Pain sensitivity (cold pain threshold)	Prospective longitudinal study (Wang et al. 2011[1])	Tapering was performed in patients with cLBP (with/without OT) and healthy controls with neither pain nor opioid therapy. (98 patients)	Significantly lower cold pain thresholds were demonstrated at 3 weeks in cLBP patients on opioids compared with opioid naïve patients (p=0.004 for hand) and healthy controls (p=0.001 for hand, p=0.021 for left low back).	Very serious study limitations (-2)	No serious inconsistency	No serious indirectness	Very serious imprecision (-2) (One single small study, imprecise description of statistical outcomes)	Very low
Tapering: 12 hr Conversion Versus 6 hr Conversion								
Pain intensity (11-point NRS)	Prospective double-blinded RCT (Nomura et al. 2011[2])	12-h conversion versus 6-h conversion (87 patients)	No significant increases were observed in pain intensity in either group. In the 12-h group, significant decreases in pain intensity were observed at 6 hours and 12 hours compared with that prior to application of the fentanyl patch (6 hours 95% CI: 0.17 to 0.63; p=0.003; 12 hours 95% CI: 0.23 to 0.84; p=0.003).	Very serious study limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (One single small study)	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
			In the 6-h group, no significant decreases in pain intensity were reported (p>0.05).					
Bolus use	Prospective double-blinded RCT (Nomura et al. 2011[2])	12-hour conversion versus 6-hour conversion (87 patients)	No significant between group differences were reported.	Very serious study limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (One single small study, no measures of dispersion)	Very low
Treatment-emergent adverse events (TEAEs)	Prospective double-blinded RCT (Nomura et al. 2011[2])	12-hour conversion versus 6-hour conversion (87 patients)	Significantly more 12-h method group (11 patients) experienced TEAEs than the 6-h method group (95% CI: 0.01 to 0.55; p=0.002)	Very serious study limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (One single small study)	Very low

[a] Methodological Quality takes into account the overall risk of bias rating of all the studies included in the evidence base;
[b] Inconsistency of results considers if the studies demonstrated similar positive or negative results (an inconsistent rating would indicate that the findings across studies were mixed);
[c] Indirectness of evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence) as well as the applicability of the study population; and
[d] Imprecision estimates the degree of uncertainty (based on variance or sample size) around an outcome's effect size.

CI: confidence interval; cLBP: chronic lower back pain; NRS: numeric rating scale; OT: opioid therapy; QST: quantitative sensory testing; RCT: randomized controlled trial

Appendix A. Evidence Tables

Table 2. Individual Studies

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Reference: Wang et al. 2011[1] **Country:** Germany **Study Design:** Prospective, longitudinal study **Purpose:** To investigate pain sensitivity in a homogeneous patient population (chronic low back pain [cLBP] patients only) after tapering of long-term (17 months) opioid use and to monitor the changes in pain sensitivity for 6 months **Quality Rating:** Fair Authors used appropriate attention to confounders in analysis but the study had less than 80% follow-up. Lack of precision in reporting statistical findings (p-values only).	**Number of Patients:** 98 patients (35 patients with both cLBP and opioid medication [OP], 35 opioid-naïve cLBP patients [ON], and 28 individuals with neither pain nor opioid intake [HC]) **Diagnosis:** cLBP **Age (Years):** Mean 47.6 years **Gender:** Women 54.1% **Inclusion Criteria:** Study included patients with cLBP who were 1) aged between 20 and 70 years; 2) had a history of at least 6 months of chronic myofascial LBP without radicular sensory or motor deficits or radicular pain symptoms (herniation or disc protrusion excluded by magnetic resonance imaging), but sick leave amounting to less than 6 months within the 12 months immediately before enrollment in this study (grade II chronification according to von Korff); 3) defined opioid therapy as intake of a morphine equivalent dose of at least 30 mg per day every day for more than 3 months. Non-opioid pain medication in the group of opioid-naïve patients was allowed. **Exclusion Criteria:** The exclusion criteria for both patient groups were: 1) sensory deficits because of diabetes, alcoholic neuropathy, spinal stenosis, or severe thyroid, liver, or kidney disease; 2) interventional pain management procedures that might alter QST responses, including neuraxial or local anesthetic block, within the previous 3 months; 3) major psychiatric disorders requiring recent hospitalization, such as schizophrenia or psychosis; and 4) infection or acute injury at the QST site.	**Treatment:** The dosage of opioid preparation was halved every 3 days until the patients became opioid clean. Data from patients who remained opioid clean at 6 months was used for statistical analysis (group 1, *N*=17; group 2, *N*=22, group 3, *N*=18). **Primary Outcome:** Sensitivity (thermal sensation and thermal pain thresholds in low back and non-dominant hand) was measured by quantitative sensory testing (QST) at 1 day before (T1), 3 weeks after (T2), and 6 months after the start of opioid tapering (T3) **Note:** For the standardized data analysis, they study used the following conversion ratios between an oral dose of morphine and other opioid analgesics: 1 mg morphine = 0.65 mg oxycodone, 0.25 mg methane, 5 mg tilidine, 0.01 mg fentanyl, 0.13 mg hydromorphone, 5 mg tramadol. **Follow-up:** 6 months	**Pain Sensitivity (Heat Pain Thresholds):** Significant differences in heat pain thresholds were found among the three groups at all three time points (T1: p=0.001, T2: p=0.015, T3: p=0.008), however no differences were reported at any time point between the two patient groups (OP and ON) At T3, the heat pain thresholds of cLBP and opioid medication patients (OP) still remained lower than HC (p=0.017), while those of cLBP and opioid naïve patients (ON) were normalized. **Pain Sensitivity (Cold Pain Thresholds):** cLBP and opioid medication patients showed lower cold pain thresholds at T2 than cLBP and opioid naive patients and HC. **Pain Sensitivity (Warm Stimuli):** Compared with T1, cLBP and opioid medication patients reacted to warm stimuli significantly faster at T2 (p=0.029), while cLBP and opioid naïve patients did not change their pain profile. At T3, cLBP and opioid medication patients showed a further increase in speed of reaction to warm stimuli (p=0.01) and a further lowering of cold pain (p=0.026) relative to T2. Statistically significant correlations were determined between sensation of warmth in the hand and both age (*r*=0.308, p=0.015) and sex (*r*=0.271, p=0.003). Moderate correlations were observed with NRS scores and thermal sensation. No correlations were observed between QST values and depression, pain duration, opioid dose, or duration. **Adverse Events:** Nausea, weakness, increased sweating, and sleep disturbance were commonly reported during week 1. The authors concluded that long-term use of opioids did not reduce pain sensitivity in cLBP patients; though opioid tapering induced brief hyperalgesia.

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Reference: Nomura et al. 2011[2] **Country:** Japan **Study Design:** Prospective, double-blinded RCT **Purpose:** To compare the safety and efficacy of a 12-h conversion method to a 6-h conversion method in chronic cancer pain management. **Quality Rating:** Poor Adequate randomization and allocation concealment methods, good matching of baseline characteristics but lacks an intent-to-treat analysis.	**Number of Patients:** 87 (12-h group = 43; 6-h group = 44) **Diagnosis:** Chronic cancer pain **Age (Years):** Mean 60.2 in 12-h group, 61.1 in 6-h group **Gender:** Men 70.1% **Inclusion Criteria:** Patients with cancer being pretreated with continuous intravenous fentanyl, age >20 years, assessable pain intensity, Numeric Rating Scale (NRS; assessed from 0 to 10) ≤5, stable cancer pain for more than 6 days or using less than three bolus doses per day were included. **Exclusion Criteria:** Patients with acute cancer pain, unstable cancer pain, difficult to assess pain intensity, unconsciousness, hepatic dysfunction (ALT or AST ≥2× upper limit of normal, bilirubin ≥2.0 mg/dl), or renal dysfunction (creatinine level ≥2.0 mg/dl) were excluded. Patients receiving a new course of chemotherapy were also excluded.	**Treatment**: Patients were randomly allocated to a conversion method from continuous intravenous infusion to transdermal fentanyl using two-step tapering of the continuous intravenous infusion in the 12-h (12-h method) or in the 6-h (6-h method) conversion. In the 12-h group, fentanyl was administered using the 12-h method, and saline was administered using the 6-h method. In the 6-h group, fentanyl was administered using the 6-h method, and saline was administered using the 12-h method. A conversion rate of 1:1 was established for switching from intravenous fentanyl to a transdermal fentanyl patch. The mean dosages of the applied fentanyl patch were - 12-hr group: 23.3±13.3 µg/h (range, 12.5 to 100 µg/h) 6-hr group: 28.3±21.4 µg/h (range, 12.5 to 100 µg/h) in the 6-h group. **Primary Outcome:** Toxicity **Secondary Outcomes:** Change in pain intensity measured by NRS, number of boluses used **Follow-up:** 6, 12, 18, 24 and 48 hours	**Pain Intensity:** No significant increases were observed in pain intensity in both groups. In the 12-h group, significant decreases in pain intensity were observed at 6 hours and 12 hours compared with that prior to application of the fentanyl patch (6 hours 95% CI: 0.17 to 0.63; p=0.003; 12 hours 95% CI: 0.23 to 0.84; p=0.003). In the 6-h group, no significant decreases in pain intensity were reported (p>0.05). **Bolus Use:** No significant differences were reported in the number of boluses used between groups. (ps>0.05, respectively) **Toxicity:** Significant differences were reported in the incidence of adverse events in the 12-h method group versus the 6-h method group (12-h group = 25.6%, 6-h group = 2.3%; 95% CI: 0.01 to 0.55; p=0.002). The incidence of opioid-related adverse events above baseline was more frequent with the 12-h method group (11 patients) than the 6-h method group (95% CI: 0.01 to 0.55; p=0.002). Adverse events, which were considered opioid-related, led to early discontinuations for 16% of patients in the 12-h method group. **Adverse Events: (12-hr)** **Somnolence** (n) Grade- 3: 2 Grade- 4: 1 **Confusion** (n) Grade- 3: 2 **Nausea** (n) Grade- 2: 1 Grade- 4: 1 **Vomiting** (n) Grade- 1: 1 **Diarrhea** (n) Grade- 2: 1 **Fatigue** (n) Grade- 1:1 Grade- 3: 1 **Adverse Events: (6-hr)** **Fatigue** (n) Grade- 2: 1 The authors reported an excellent safety profile and sustained efficacy were demonstrated for the 6-h conversion method.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; cLBP: chronic lower back pain; HC: hydrocodone; mg: milligram; NRS: numeric rating scale; ON: opioid-naïve; OP: opioid medication; QST: quantitative sensory testing; RCT: randomized controlled trial; ug/h: microgram/hour

Appendix B. References

1. Wang H, Akbar M, Weinsheimer N, Gantz S, Schiltenwolf M. Longitudinal observation of changes in pain sensitivity during opioid tapering in patients with chronic low-back pain. Pain Med. 2011 Dec;12(12):1720-6. Also available: http://dx.doi.org/10.1111/j.1526-4637.2011.01276.x. PMID: 22082225
2. Nomura M, Kamata M, Kojima H, Hayashi K, Kozai M, Sawada S. Six- versus 12-h conversion method from intravenous to transdermal fentanyl in chronic cancer pain: a randomized study. Support Care Cancer. 2011 May;19(5):691-5. Also available: http://dx.doi.org/10.1007/s00520-010-0890-1. PMID: 20549247
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4. Pedersen L, Borchgrevink PC, Breivik HP, Fredheim OMSÃ¸. A randomized, double-blind, double-dummy comparison of short- and long-acting dihydrocodeine in chronic non-malignant pain. Pain. 2014 May;155(5):881-8. Also available: http://dx.doi.org/10.1016/j.pain.2013.12.016. PMID: 24345428
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Appendix C. Excluded Studies

Table 3. Excluded Studies

Reference	Reason for Exclusion
Berna C et al. 2015[3]	Not a systematic review or clinical trial of any design
Imanaka K et al. 2014[4]	Condition is not chronic pain
Blondell et al. 2010[5]	Fewer than 20 patients enrolled

Appendix A: Literature Search Methods

Resources Searched

ECRI Institute information specialists searched the following databases for relevant information. Search terms and strategies for the bibliographic databases appear below.

Name	Search Dates	Platform/Provider
Agency for Healthcare Research and Quality (AHRQ)	Searched November 23, 2015	U.S. Department of Health & Human Services
Centers for Disease Control and Prevention (CDC)	Searched November 30, 2015	www.cdc.gov
Cochrane Library	Searched November 5, 2015	John Wiley & Sons, Ltd.
EMBASE (Excerpta Medica)	January 1, 2009 on	
Google	Searched November 23, 2015	www.google.com
Healthcare Standards (HCS)	Searched November 30, 2015	ECRI Institute
Medline	January 1, 2009 on	OVID Technologies, Inc.
National Guideline Clearinghouse (NGC)	Searched November 30, 2015	Agency for Healthcare Research and Quality (AHRQ)
National Institute for Health and Care Excellence (NICE)	Searched November 23, 2015	National Institute for Health and Care Excellence
PsycINFO	January 1, 2009 on	OVID Technologies, Inc.
PubMed (In-process, Publisher, and PubMedNotMeSH records)	Searched October 22, 2015 and January 11, 2016	National Library of Medicine (NLM)

Hand Searches of Journal and Gray Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included feedback and recommendations from work group members and review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Topic-specific Search Terms

The vocabulary presented in this table includes controlled vocabulary and free-text keywords for bibliographic database searches performed in EMBASE, Medline, and PsycINFO. Strategies for selected databases follow this table.

EMTREE, Medical Subject Headings (MeSH), PsycINFO, and Keywords

The strategies below are presented in Embase.com and OVID syntaxes. Embase.com was used to search for EMBASE (EMTREE) and Medline records. OVID was used to search PsycINFO.

Specific search strings were used to capture studies based on the key questions identified by the COT working group. Unique strategies were structured for each concept addressed by the key questions. These search results were further refined to capture specific study designs, publication types, date ranges, English language studies, and to exclude out-of-scope citations.

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Patient Population		
Chronic Pain	**EMBASE** 'chronic disease'/exp 'chronic inflammatory pain'/exp 'chronic pain' 'pain'/exp **MeSH** exp chronic disease/ exp pain/ **PsycINFO** Exp chronic illness/ exp chronic pain/ exp pain/	chronic Chronic adj3 pain* Chronic NEXT/3 pain* Long?term NEXT/3 pain* months pain weeks year*
Chronic Opioid Use	**EMBASE** 'analgesic agent'/exp 'codeine'/de 'drug therapy'/lnk 'fentanyl'/de 'morphine'/de 'narcotic agent'/exp 'narcotics'/exp 'narcotic drugs'/exp 'opiate'/de 'opiates'/exp **MeSH** Chronic pain/drug therapy exp analgesics, opioids exp narcotics **PsycINFO** exp analgesic drugs exp narcotics	Analgesic* COT 'chronic NEXT/1 opi* NEXT/1 therapy' 'chronic opi* therapy' codeine Fentanyl heroin Hydrocodone Hydromorphone Long?term Methadone months morphine narcotic* Opi* Oxycodone Oxycontin

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	exp narcotic drugs exp opiates	Oxymorphone percocet Tapentadol Tramadol Vicodin weeks Year*
KQ1 **Contraindications** What is the evidence that the following medical or mental health conditions are absolute or relative contraindications of prescribing COT? • Active pursuit of compensation • Centralized pain conditions such as fibromyalgia • Chronic obstructive pulmonary disease • Cognitive impairment • Depression • Headache • GI motility problems (e.g., toxic megacolon, GI pain syndromes, narcotic bowel syndrome) • Immune status changes • Inability to participate in comprehensive treatment plan • Incarceration (history of) • Hepatic, renal, or pulmonary disease • Suspected opioid misuse (e.g., overdose, early refills, diversion, taking more than prescribed) • Osteoporosis • Personality disorders • Posttraumatic stress disorder • Sleep disorders • SUD (current or history of)—include specific disorders and appropriate key words in search • Suicidality • Traumatic brain injury • Use of medical marijuana • QT prolongation	**EMBASE** 'drug contraindication'/exp 'drug interaction'/exp 'drug safety'/exp **MeSH** analgesics, opioid/contraindications Polypharmacy/ **PsycINFO** Drug interactions/ Polypharmacy/ Safety/	Cardiovascular CNS COPD Compensation* Contraindication* depression Fibromyalgia gastrointestinal Headache* Heart immune Liver Lung Obstructive Osteoporosis (personality or cognitive or mental or neuro*) adj3 (disorder* or disease* or illness*)) Post?traumatic stress PTSD Respiratory Sleep Substance adj2 (abuse OR misuse) Substance use disorder SUD Suicide suicidality TBI Traumatic brain

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
KQ2 **Risk factors for the continuum of misuse or OUD** What factors increase the risk of developing misuse or OUD when considering COT?	**EMBASE** 'analgesic agent abuse'/exp 'bullying'/exp 'opiate addiction'/exp 'opioid-related disorders'/exp 'risk'/exp 'sexual abuse'/exp **MeSH** 'bullying'/ 'domestic violence'/exp 'risk assessment'/exp 'substance-related disorders'/exp **PsycINFO** Exp addiction/ Exp at risk populations/ Exp codependency/ Exp drug abuse/ Exp drug addiction/ Exp drug overdoses/ Exp illegal drug distribution/ Exp risk assessment/ Exp risk factors Exp risk perception/	Abuse Addict* Assess* Bully Bullying dependency Disorder* Overdose* Predict* Risk* violence
KQ3 AND KQ4 **Effectiveness of COT** What is the comparative effectiveness of COT versus other treatment modalities? a. What is the comparative effectiveness of COT versus other treatment modalities for patients with a history of or current SUD? **Safety of COT** What is the safety of COT versus other treatment modalities? a. What is the safety of COT versus other treatment modalities for patients with a history of or current SUD?	**EMBASE** 'adverse drug events'/exp 'adverse drug reaction'/exp 'adverse drug reaction'/lnk 'patient safety'/exp 'prescription drugs'/exp 'side effect'/lnk 'side effect'/de 'treatment outcome'/de **MeSH** 'analgesics, opioid'/*adverse effects 'prescription drugs'/adverse effects 'quality of life' 'risk' 'side effect'/de 'treatment outcome' **PsycINFO** *quality of life/	Aberrant NEXT/3 behavior* Absence absent Abuse Accident* 'ade' Addict* adverse 'adverse drug events' Adverse NEXT/1 effect* Anxiety cardiac cardiovascular cognitive complication depression Diversion effective

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	"side effects (drug)"/ *treatment outcomes/ Drug overdose/*prevention & control	effectiveness Fall Falls Misuse Mood Outcome* Overdose 'pain relief' Pain NEXT/2 relief Pain NEXT/3 reliev* 'quality of life' QOL Safety 'side effect*' Sleep s
KQ5 **Effectiveness of different opioid formulations** What is the comparative effectiveness and safety of various opioid formulations? a. Immediate-release/short-acting opioids compared to extended-release/long-acting opioids b. Route of administration/ delivery alternatives such as transdermal, buccal, sublingual, pumps c. Abuse deterrent formulations compared to non-abuse deterrent formulations d. Tramadol and other dual-mechanism opioids e. Buprenorphine f. Methadone	**EMBASE** 'short acting analgesic agent'/exp **MeSH** 'analgesics, short-acting' **PsycINFO** *drug therapy	Abuse-deterrent controlled 'controlled release' extended 'extended release' Formulation immediate 'immediate release' LA 'long?acting' Medication Medicine Pill* Prescription* SA 'short?acting' (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)) Sustained
KQ6 **Added benzodiazepines** Does additional use of benzodiazepines or other psychoactive medications increase the risk of adverse events compared to opioid therapy alone?	**EMBASE** 'antidepressant agent'/exp 'benzodiazepine' 'benzodiazepine derivative'/exp 'hypnotic sedative agent'/exp 'narcotic analgesic agent'/exp	Ambien 'anti depressant' Antidepressant* Anti-depressant' Benzodiazepine* 'eszopiclone'

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	'non prescription drug' 'prescription drug' **MeSH** 'patient safety' 'polypharmacy'/exp 'safety' **PsycINFO** exp analgesic drugs/ Exp anesthetic drugs/ Exp anticonvulsive drugs/ Exp antidepressant drugs/ Exp antiemetic drugs/ Exp antihistaminic drugs/ Exp antihypertensive drugs/ exp benzodiazepines/ exp cns depressant drugs/ drug therapy/sh *hypnotic drugs/ Insomnia.id. Major depression.id. Exp polypharmacy/ Schizophrenia.id. Exp sedatives/ Exp self medication/	Hypnotic* lunesta OTC 'over-the-counter' 'over the counter' prescription* polypharmacy psychoactive* sonata stimulant* 'z drug' 'z drugs' 'zaleplon' 'zolpidem'
KQ7 **Risk mitigation strategies** What is the comparative effectiveness of different risk mitigation strategies for patients either on COT or being considered for COT? a. Does this differ for patients with history of or current SUD? b. Does this differ for patients with mental health comorbidities? c. Does this differ for patients with medical comorbidities?	**EMBASE** 'opiate addiction'/exp 'patient education'/exp 'prescription drug diversion'/exp 'risk reduction'/exp 'substance abuse'/exp 'urinalysis'/exp **MeSH** 'contracts' 'drug monitoring' exp 'patient compliance'/ exp 'risk'/ **PsycINFO** exp addiction/ Exp client education/ exp drug abuse/ drug abuse.sh. exp drug addiction/	Abuse Addict* agreement 'call back' Call-back Compliance comply consent contract database diversion divert doctor Detect* Diversion Divert Misuse Monitor*

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	opiates.id. exp monitoring/ exp patient compliance/ Exp prescription drugs/ Exp risk assessment/ Exp risk evaluation and mitigation strategy/ Exp risk perception/ Exp treatment compliance/	Naloxone NEXT/2 rescue office Pill NEXT/2 count physician primary Query Recall Risk* Screen* surveillance Test* Urin*
KQ8 **Treatment of OUD** What is the safety and effectiveness of treatment of OUD (diagnosed or suspected) in patients with chronic pain? a. Do outcomes vary by severity of OUD?	**EMBASE** 'acceptance and commitment therapy'/exp 'addiction'/exp 'analgesic agent abuse'/exp 'cognitive therapy'/exp 'drug abuse'/exp 'drug dependence'/exp 'narcotic analgesic agent'/exp 'narcotic dependence'/exp 'opiates'/exp 'opiate addiction'/exp 'psychotherapy'/exp 'support group'/exp **MeSH** 'analgesics, opioid'/exp 'cognitive therapy'/exp 'counseling'/exp 'motivational interviewing'/ 'narcotics'/exp 'substance abuse detection'/exp 'substance-related disorders'/exp **PsycINFO** exp addiction/ Exp adjunctive treatment/ Exp cognitive therapy/ Exp counseling/ exp drug abuse/ drug abuse.sh. exp drug addiction/ exp drug dependence/	aberrant Abuse Addict* Behavioral buprenorphine Cognitive Contingency 'contingency management' Counsel* counseling drug interview* methadone misuse motivation* naltrexone therapy treat* treatment

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	electrosleep treatment/ exp motivational interviewing/ exp opiates/ opiates.id. Exp prescription drugs/ Exp psychotherapy/ Exp support group/ Exp treatment/ Exp treatment compliance/ Exp treatment effectiveness evaluation/ Exp treatment outcomes/	
KQ9 **Tapering** What is the safety and effectiveness of different tapering strategies and schedules?	**EMBASE** 'analgesia'/exp 'clinical protocol'/exp 'dose response'/exp 'drug administration'.exp 'drug therapy'/lnk 'pain management'/exp **MeSH** 'clinical protocols'/exp 'drug administration schedule'/exp **PsycINFO** exp analgesic drugs/ Exp drug dosages/ Exp pain management/	Adjust* administration Decrease* Dose Dosing plan protocol Reduc* Schedule Strategy strategies Taper* Titrat*

EMBASE Conventions:

* (within or following a term) = truncation character (wildcard)

:ab = limit to abstract

:ab,ti = limit to abstract and title

NEAR/n = search terms within a specified number (*n*) of words from each other in any order

/exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

:it. = limit to publication type

:ti. = limit to title

EMBASE/Medline Search Strategies conducted using Embase.com Syntax

Set #	Concept	Search Statement
1	Chronic pain	'chronic pain'/exp OR (chronic OR 'long term') NEXT/2 pain*
2		'chronic inflammatory pain'/de OR (chronic NEXT/3 pain*):ab,ti.
3	Combine sets for chronic pain	1 OR 2
4	COT	'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de
5		opioid* OR opiod* OR opiate* OR oposal OR opon OR narcotic*
6		'morphine'/de OR 'codeine'/de OR 'fentanyl'/de
7		Oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol
8		'pain'/exp AND 'drug therapy'/lnk AND opi*
9	Combine sets for opioids	4 OR 5 OR 6 OR 7 OR 8
10	Combine with chronic	9 AND (chronic:ti OR 'cot':ti OR chronic NEXT/1 opi* NEXT/1 therapy OR longterm:ti OR 'long term':ti OR months:ab,ti OR year*:ab,ti)
11	Combine chronic pain with COT	3 AND 10
12	Contraindications (KQ1)	'drug contraindication'/exp OR 'drug interaction'/exp OR 'drug safety'/exp OR 'analgesics, opioid/contraindicaitons'
13		Compensation* OR contraindication* OR copd OR cardiovascular OR respiratory OR 'chronic obstructive' OR lung OR fibromyalgia OR headache* OR heart OR liver OR sleep OR osteoporosis OR cns OR immune OR gastrointestinal OR medic* NEAR/1 marijuana OR 'post-traumatic stress' OR ptsd OR 'traumatic brain' OR tbi OR 'substance use disorder' OR sud OR depression OR suicide OR suicidality OR (personality OR cognitive OR mental OR neuro*) NEXT/3 (disorder* OR disease* OR illness*)
14	Combine contraindications	12 OR 13
15	Combine contraindications with chronic pain and COT	11 AND 14
16	Risk of misuse (KQ2)	('opiate addiction'/exp OR 'analgesic agent abuse'/exp OR 'opioid-related disorders'/exp) AND ('risk'/exp OR risk*:ab,ti)
17		'risk'/exp OR (risk* AND (predict* OR assess*))
18		(opi* OR narcotic* OR hydrocodone OR vicodin OR oxycodone OR oxycontin OR percocet OR heroin OR methadone OR morphine OR codeine OR analgesic*) NEXT/2 (addict* OR abuse OR misuse OR disorder OR diversion)
19	History of abuse	'domestic violence'/exp OR 'sexual abuse'/exp OR 'bullying'/exp OR bully OR bullying OR (domestic OR spous* OR child* AND (abuse OR violence))
20	Risk of opioid addiction	17 AND (18 OR 19)
21	Combine risk sets	16 OR 20
22	Combine risk of misuse with chronic pain and COT	11 AND 21
23	Effectiveness and Safety of COT (KQs 3 and 4)	'adverse drug events' OR 'ade' OR overdose OR diversion OR misuse OR addict* OR abuse OR adverse NEXT/1 event OR adverse NEXT/1 effect* OR accident* OR absence OR absent OR falls OR fall OR depression OR anxiety OR mood OR sleep OR aberrant NEXT/3 behavior* OR complication* OR cardiovascular OR cardiac OR cognitive

Set #	Concept	Search Statement
24		'quality of life'/exp OR 'quality of life' OR qol OR pain NEXT/2 relief OR pain NEXT/2 reliev* OR 'pain relief'
25		'prescription drugs'/exp AND ('adverse drug reaction'/lnk OR 'side effect'/lnk)
26		'treatment outcome'/de OR 'side effect'/de OR 'adverse drug reaction'/exp OR 'patient safety'/exp OR safety OR effectiveness OR effective OR outcome*
27	Combine sets for safety	23 OR 24 OR 25 OR 26
28	Combine with chronic pain and COT	11 AND 27
29	Formulations (KQ5)	'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de
30		opioid* OR opiod* OR opiate* OR oposal OR opon OR narcotic* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol
31		'morphine'/de OR 'codeine'/de OR 'fentanyl'/de
32		'pain'/exp AND 'drug therapy'/lnk AND opi*
33	Combine sets for opioids	29 OR 30 OR 31 OR 32
34		'immediate release' OR 'extended release' OR 'short acting' OR shortacting OR sa OR 'long acting' OR longacting OR la OR 'controlled release' OR (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)) OR 'short acting analgesic agent'/exp OR (abuse-deterrant AND formula*)
35		33 AND 34
36		'opiate'/exp OR 'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de OR morphine OR oxycodone OR oxymorphone OR opi* AND (controlled OR sustained OR extended)
37	Opioid formulations	35 OR 36
38	Combine with chronic pain and COT	11 AND 37
39	Added benzodiazepines (KQ6)	'benzodiazepine derivative'/exp OR 'benzodiazepine' OR benzodiazepine* OR 'antidepressant agent'/exp OR 'hypnotic sedative agent'/exp OR 'narcotic analgesic agent'/exp OR 'benzodiazepine derivative'/exp OR 'zolpidem'/exp OR 'zaleplon'/exp OR 'eszopiclone'/exp
40		'zolpidem' OR 'zaleplon' OR 'eszopiclone' OR ambien OR lunesta OR sonata OR benzodiazepine* OR antidepressant* OR 'anti-depressant' OR 'anti depressant' OR stimulant* OR 'z drug' OR 'z drugs' OR hypnotic* OR psychoactive*
41		prescription* AND (otc OR 'over the counter') AND (multiple* OR added OR additional OR several OR concomitant)
42		'prescription drug'/exp AND 'non prescription drug'/exp OR 'polypharmacy'/exp
43	Combine medicine sets	38 OR 39 OR 40 OR 41
44		'treatment outcome'/de OR 'side effect'/de OR 'adverse drug reaction'/exp OR 'patient safety'/exp OR safety OR effectiveness OR effective OR outcome*
45	Combine with outcomes	42 AND 43
46	Combine with chronic pain and COT	11 AND 45

Set #	Concept	Search Statement
47	Risk mitigation for addiction (KQ7)	'opiate addiction'/exp OR 'substance abuse'/exp OR 'drug monitoring'/exp OR 'prescription drug diversion'/exp OR ((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol))
48		urin* NEXT/7 (screen* OR test* OR detect* OR anal* OR monitor*) OR 'urinalysis'/exp
49		pill NEXT/2 count OR 'call back' OR database OR query OR compliance OR contract* OR agreement OR consent OR recall OR surveillance OR call-back OR monitor* OR naloxone NEXT/2 rescue
50		'patient compliance'/exp OR (patient:ab,ti AND (compliance:ab,ti OR comply:ab,ti))
51		'patient education'/exp OR patient NEXT/3 (aware* OR educat*)
52		(office OR doctor OR primary) NEXT/3 (visit* OR appointment* OR check*)
53		'contracts'/exp OR opi* NEXT/5 (contract OR contracts OR agreement)
54		Risk* NEXT/7 (mitigate* OR reduc*) OR 'risk'/exp OR 'risk reduction'/exp OR 'risk evaluation and mitigation strategy'
55	Combine risk mitigation strategies	47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54
56	Combine with chronic pain and COT	11 AND 55
57	Treatment of OUD (KQ8)	addict* OR abuse OR misuse OR disorder AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol) OR 'opiate use disorder'
58		'opiate addiction'/exp OR 'analgesic agent abuse'/exp OR ('drug abuse'/exp OR 'drug dependence'/exp OR 'narcotic dependence'/exp OR 'addiction'/exp OR aberrant:ti OR aberrant:ab AND ('narcotic analgesic agent'/exp OR 'opiates'/exp OR opioid* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol OR analgesic*))
59		'psychotherapy'/exp OR 'cognitive therapy'/exp OR 'counseling'/exp OR 'acceptance and commitment therapy'/exp OR 'support group'/exp OR 'motivational interviewing'/exp
60		counsel OR counseling OR (cognitive OR contingency OR drug OR behavioral OR motivational) NEAR/2 (counseling OR therapy) OR 'contingency management' OR motivation* NEAR/1 interview* OR buprenorphine OR naloxone OR methadone
61	Combine opioid addiction set	57 OR 58
62	Combine counsel set	59 OR 60
63	Combine with chronic pain and COT	11 AND 61 AND 62
64	Tapering (KQ9)	'pain management'/exp OR 'analgesia'/exp AND ('drug administration'/exp OR 'clinical protocol'/exp)
65		'dose response'/exp OR ((dose OR dosing) AND (protocol* OR administration OR plan* OR schedule* OR strategy OR strategies))

Set #	Concept	Search Statement
66		(taper* OR decrease* OR reduc* OR adjust* OR titrat* OR dosing OR dose*) AND (protocol* OR administration OR plan* OR schedule* OR strategy OR strategies)
67	Combine tapering sets	64 OR 65 OR 66
68	Combine with chronic pain and COT	11 AND 67
69	Combine all final sets	15 OR 22 OR 28 OR 38 OR 46 OR 56 OR 63 OR 68
70	Apply limits	69 AND [2009-2016]/py AND [English]/lim AND [humans]/lim
71	Apply unwanted publication types	70 NOT ('conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)
72	Apply trials hedge	71 AND (random*:ab,ti OR trial* OR control* OR cohort OR compar*:ab,ti OR prospective OR retrospective OR series OR review* OR study OR studies OR method* OR analysis OR systematic*:ab,ti)
73		71 AND ('clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'longitudinal study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial'/de OR 'comparative study'/exp OR 'methodology'/exp)
74		71 AND ('meta analysis'/de OR 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'outcomes research'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR 'systematic review'/de OR 'meta? analysis':ab,ti OR 'systematic review':ab,ti)
75	Combine	72 OR 73 OR 74

OVID Conventions:

* (within or following a term) = truncation character (wildcard)

.ab. = limit to abstract

ADJn = search terms within a specified number (*n*) of words from each other in any order

exp/ = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.ti,ab. = limit to title and abstract fields

PsycINFO Search Strategies Presented in OVID Syntax

Set #	Concept	Search Statement
1	Chronic pain	*exp chronic pain/ OR (exp pain/ AND (chronic OR long?term)) OR (exp chronic illness/ AND pain?)
2		Chronic adj3 pain?.ti,ab.
3	Combine	1 OR 2
4	COT	exp analgesic drugs/ or exp narcotics/ or exp narcotic drugs/ or exp opiates/

Set #	Concept	Search Statement
5		(opioid* or opiod* or opiate* or oposal or opon or narcotic*).mp. OR (morphine or codeine or fentanyl).mp.
6		(Oxymorphone or tapentadol or methadone or fentanyl or hydrocodone or oxycodone or codeine or morphine or hydromorphone or tramadol).mp.
7	Combine	4 OR 5 OR 6
8	Combine chronic pain and COT	3 AND 7
9	Contraindicaitons (KQ1)	(Contraindication or COPD or cardiovascular or respiratory or obstructive or lung or fibromyalgia or headache or heart or liver or sleep or osteoporosis or CNS or immune or gastrointestinal).mp.
10		(medic* adj1 marijuana).mp. or ("post?traumatic stress" or PTSD).mp. or traumatic brain.mp. or TBI.ti,ab. or (substance adj2 abuse).mp. or (substance adj2 misuse).mp. or (depression or suicide or suicidality).mp. or ((personality or cognitive or mental or neuro*) adj3 (disorder* or disease* or illness*)).mp.
11		9 OR 10
12	Workers compensation	exp litigation/ or exp workers' compensation insurance/ or lawsuit.mp. or litigation.mp. exp insurance/ or insurance claim.mp. or exp disability evaluation/ or exp malingering/ or malingering.mp.
13		(worker adj2 compensation).mp. or litigation.ti. or lawsuit.ti. or claim*.ti. or disability*.ti. or compensation.ti. or malinger*.ti.
14	combine	11 OR 12 OR 13
15	Combine with chronic pain and COT	8 AND 14
16	Risk of misuse (KQ2)	Exp drug abuse/ or exp addiction/ or exp codependency/ or exp drug addiction/ or exp drug overdoses/ or exp illegal drug distribution/
17		16 AND (opi* or narcotic* or hydrocodone or vicodin or oxycodone or oxycontin or percocet or heroin or methadone or morphine or codeine or analgesic*).mp.
18		((opi* or narcotic* or hydrocodone or vicodin or oxycodone or oxycontin or percocet or heroin or methadone or morphine or codeine or analgesic*) adj2 (addict* or abuse or misuse or disorder* or diversion)).mp.
19		Risk*.mp. or exp risk assessment/ or exp risk perception/ or exp at risk populations/ or exp risk factors/
20		17 OR 18
21	Combine risk and abuse	19 AND 20
22	Combine with chronic pain and COT	8 AND 21
23	Effectiveness and Safety of COT (KQs 3 and 4)	exp "Side Effects (Drug)"/ or exp "side effects (treatment)"/ or exp "complications (disorders)"/
24		exp Suicide/ or exp Major Depression/ or exp Attempted Suicide/ or exp Drug Abuse/ or exp Drug Overdoses/ or exp Drug Addiction/ or exp Safety/ or overdose.mp. or adverse events.mp. or drug addiction.mp.
25		Exp pain management/ or (pain adj2 (reliev* or relief)) or exp Quality of Life/ or quality of life.mp. or exp treatment outcomes/ or outcomes.mp.
26		((adverse adj1 event*) or (adverse adj1 effect*) or (aberrant adj3 behavior*)).mp. or (overdose* or diversion or addict* or abuse or accident* or complication* or absence or absent or falls or fall or depression or anxiety or mood or sleep or cardiovascular or cardiac or cognitive).ab,ti.

Set #	Concept	Search Statement
27		((work or occupation* or job) adj3 (injur* or accident or absence or performance)).mp. or exp safety/ or exp occupational safety/ or exp accidents/ or exp job performance/ or exp employee absenteeism/ or exp cognitive processes/ OR exp cognitive impairment/
28		exp driving behavior/ or exp drivers/ or exp risk taking/ or exp risk perception/ or exp highway safety/ or exp motor traffic accidents/ or exp motor vehicles/ or exp transportation accidents/ or exp motor traffic accidents/ or (accident* or crash or collison or wreck).mp. or ((drive or driving or car* or traffic or vehicle*) and (safe* or accident* or crash* or wreck* or impair* or risk* or collison*)).mp.
29	Combine	23 OR 24 OR 25 OR 26 OR 27 OR 28
30	Combine with COT	7 AND 29
31	Formulations (KQ5)	(*drug therapy/ or (prescription* or medication or medicine or pill*).mp. AND opi*
32		'immediate release' OR 'extended release' OR 'short acting' OR shortacting OR sa OR 'long acting' OR longacting OR la OR 'controlled release' OR (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)).mp.
33		(formulation* or short?act* or long?act* or immediate or extended or controlled or sustained or abuse-deterrent or (abuse adj1 deterrent)).mp.
34		(opiate* or opioid).ti. and (formulation* or short?act* or long?act* or immediate or extended or controlled or sustained).mp.
35	Combine	(31 AND (32 OR 33)) OR 34
36	Combine with COT	7 AND 35
37	Added benzodiazepines (KQ6)	benzodiazepine*.mp. or exp benzodiazepines/
38		*hypnotic drugs/ or exp analgesic drugs/ or exp anesthetic drugs/ or exp anticonvulsive drugs/ or exp antiemetic drugs/ or exp antihistaminic drugs/ or exp antihypertensive drugs/ or exp benzodiazepines/ or exp cns depressant drugs/ or exp sedatives/ or exp antidepressant drugs/ or exp nonprescription drugs/ or exp self medication/ or exp prescription drugs/ or exp polypharmacy/
39		(insomnia or chronic pain or schizophrenia or major depression).id. and drug therapy.sh.
40		(zolpidem or zaleplon or eszopiclone or ambien or lunesta or sonata or benzodiazepine* or antidepressant* or anti-depressant* or stimulant* or 'z drug' or 'z drugs' or hypnotic* or psychoactive*).mp.
41		(over-the-counter or 'over the counter' or OTC).mp or (prescription* or prescribed).ab,ti. Or polypharmacy.mp.
42		((medication* or medicine) and (multiple or concomitant or several)).mp.
43	Combine	37 OR 38 OR 39 OR 40 OR 41 OR 42
44	Combine with chronic pain and COT	8 AND 43
45	Risk mitigation for addiction (KQ7)	exp opiates/ or exp drug addiction/ or exp prescription drugs/ or exp drug abuse/ or exp addiction/ OR (opiates.id and drug abuse.sh.)
46		((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol)).mp.
47	Combine opiate addiction or misuse	45 OR 46

Set #	Concept	Search Statement
48	Mitigation strategies	urin* adj7 (screen* OR test* OR detect* OR anal* OR monitor*) OR exp urinalysis/ or exp drug usage screening/
49		Count OR 'call back' OR database OR query OR compliance OR contract* OR agreement OR consent OR recall OR surveillance OR call-back OR monitor* OR ('pill count' OR pill count).mp.
50		(naloxone adj2 rescue).mp.
51		'patient compliance'/exp OR (patient:ab,ti AND (compliance:ab,ti OR comply:ab,ti))
52		Exp treatment compliance/ or (patient and (compliance or comply)).ab,ti.
53		((office OR doctor OR primary) adj3 (visit* OR appointment* OR check*)).mp. OR (exp opiates/ AND exp monitoring/)
54		Exp client education/ or patient education.mp. OR patient NEXT/3 (aware* OR educat*)
55		(opi* adj5 (contract OR contracts OR agreement)).mp.
56	Combine mitigation strategies	48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55
57	Risk	Exp risk assessment/ or exp risk perception/ or (risk* adj7 (mitigate* OR reduc*)).mp. or (risk evaluation and mitigation strategy).mp.
58	Combine addiction, mitigation, and risk	47 AND 56 AND 57
59	Combine addiction, mitigation, and risk with COT	7 AND 58
60	Treatment of OUD (KQ8)	((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol)).mp.
61	Opiate addiction or misuse	exp opiates/ or exp drug addiction/ or exp prescription drugs/ or exp drug abuse/ or exp addiction/ OR (opiates.id and drug abuse.sh.)
62		(exp drug abuse/ or exp drug dependence/ or exp drug addiction/ or aberrant.ti. or aberrant.ab.) and (exp opiates/ or opioid*.mp. or oxymorphone.mp. or tapentadol.mp. or methadone.mp. or fentanyl.mp. or hydrocodone.mp. or oxycodone.mp. or codeine.mp. or morphine.mp. or hydromorphone.mp. or tramadol.mp. or analgesic*.mp.)
63	Counseling	Exp psychotherapy/ OR exp cognitive therapy/ OR exp counseling/ OR exp support group/ OR exp motivational interviewing/ exp Adjunctive Treatment/ or exp Treatment Compliance/ or exp Treatment/ or exp Treatment Effectiveness Evaluation/ or (treat or treatment or therap* or counsel*s).ab,ti.
64		counsel OR counseling OR ((cognitive OR contingency OR drug OR behavioral OR motivational) adj2 (counseling OR therapy)) OR motivation* adj1 interview* OR (buprenorphine OR naloxone OR naltrexone OR methadone) OR contingency management.mp.
65	Combine addiction	60 OR 61 OR 62
66	Combine counseling	63 OR 64
67	Combine COT and addiction and counseling	7 AND 65 AND 66
68	Tapering (KQ9)	(exp analgesia/ or exp analgesic drugs/ or exp pain management/) AND exp drug dosages/
69		((dose or dosing) and (protocol* or administration or plan* or schedule* or strategy or strategies)).mp.

Set #	Concept	Search Statement
70		(taper* or decrease* or reduc* or adjust* or titrat* or dosing or dose*).mp.
71		((taper* or decrease* or reduc* or adjust* or titrat* or dosing or dose*) and (protocol* or administration or plan* or schedule* or strategy or strategies)).mp.
72	Combine tapering sets	68 OR 69 OR 70 OR 71
73	Combine tapering and chronic pain and COT	8 AND 72
74	Combine all final sets	15 OR 22 OR 30 OR 36 OR 44 OR 59 OR 67 OR 73
75	Apply limits	limit 74 to (human and english language and yr="2009 - 2016")
76	Apply publication type limits	75 AND (trial* or study or studies or method* or review* or analysis or compar* or random* or systematic*).mp.
77		limit 75 to ("0100 journal" or "0110 peer-reviewed journal" OR “journal article”)
78		75 AND (exp clinical trials/ or exp cohort analysis/ or exp followup studies/ or exp longitudinal studies/ or ((compar* or comparison or comparative) and trial*).ab,ti.
79	Combine final sets	76 OR 77 OR 78

Appendix B. List of All Included Studies by Key Question

Key Question 1: What is the evidence that various medical or mental health conditions are absolute or relative contraindications of prescribing COT?

Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011 Apr 6;305(13):1315-21. Also available: http://dx.doi.org/10.1001/jama.2011.370. PMID: 21467284

Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS, Stewart WF. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. Addiction. 2010 Oct;105(10):1776-82.

Campbell G, Bruno R, Darke S, Degenhardt L. Associations of borderline personality with pain, problems with medications and suicidality in a community sample of chronic non-cancer pain patients prescribed opioids for pain. Gen Hosp Psychiatry. 2015 Sep 1;37(5):434-40. Also available: http://dx.doi.org/10.1016/j.genhosppsych.2015.05.004.

Campbell G, Nielsen S, Larance B, Bruno R, Mattick R, Hall W, Lintzeris N, Cohen M, Smith K, Degenhardt L. Pharmaceutical opioid use and dependence among people living with chronic pain: associations observed within the pain and opioids in treatment (POINT) cohort. Pain Med. 2015 Sep 1;16(9):1745-58. Also available: http://dx.doi.org/10.1111/pme.12773.

Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. Clin J Pain. 2014 Jul;30(7):557-64. Also available: http://dx.doi.org/10.1097/AJP.0000000000000021. PMID: 24281273

Huffman KL, Shella ER, Sweis G, Griffith SD, Scheman J, Covington EC. Nonopioid substance use disorders and opioid dose predict therapeutic opioid addiction. J Pain. 2015 Feb;16(2):126-34.

Im JJ, Shachter RD, Oliva EM, Henderson PT, Paik MC, Trafton JA, PROGRES Team. Association of care practices with suicide attempts in US veterans prescribed opioid medications for chronic pain management. J Gen Intern Med. 2015 Jul;30(7):979-91. Also available: http://dx.doi.org/10.1007/s11606-015-3220-y. PMID: 25693651

Price C, Wobeter B, Delate T, Kurz D, Shanahan R. Methadone for pain and the risk of adverse cardiac outcomes. J Pain Symptom Manage. 2014 Sep;48(3):333-42.

Seal KH, Shi Y, Cohen G, Cohen BE, Maguen S, Krebs EE, Neylan TC. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. JAMA: Journal of the American Medical Association. 2012 May 7;307(9):940-7.

Shah RD, Cappiello D, Suresh S. Interventional procedures for chronic pain in children and adolescents: a review of the current evidence. Pain Pract. 2016 Mar;16(3):359-69. Epub 2015 Mar 6. Also available: http://dx.doi.org/10.1111/papr.12285.

Turner BJ, Liang Y. Drug overdose in a retrospective cohort with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: interactions with mental health disorders. J Gen Intern Med. 2015 Aug 28;30(8):1081-96. Also available: http://dx.doi.org/10.1007/s11606-015-3199-4.

Turner JA, Saunders K, Shortreed SM, LeResche L, Riddell K, Rapp SE, Von Korff M. Chronic opioid therapy urine drug testing in primary care: prevalence and predictors of aberrant results. J Gen Intern Med. 2014;29(12):1663-71. Also available: http://dx.doi.org/10.1007/s11606-014-3010-y.

Wasan AD, Michna E, Edwards RR, Katz JN, Nedeljkovic SS, Dolman AJ, Janfaza D, Isaac Z, Jamison RN. Psychiatric comorbidity is associated prospectively with diminished opioid analgesia and increased opioid misuse in patients with chronic low back pain. Anesthesiology. 2015 Oct 1;123(4):861-72. PMID: 26375824

Yarlas A, Miller K, Wen W, Lynch SY, Munera C, Dain B, Pergolizzi JV, Raffa R, Ripa SR. A subgroup analysis found no diminished response to buprenorphine transdermal system treatment for chronic low back pain patients classified with depression. Pain Pract. 2015 Apr. Epub ahead of print. Also available: http://dx.doi.org/10.1111/papr.12298.

Key Question 2: What factors increase the risk of developing misuse or OUD when considering COT?

Banta Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain-development of a typology of chronic pain patients. Drug Alcohol Depend. 2009 Sep 1;104(1):34-42. Also available: http://dx.doi.org/10.1016/j.drugalcdep.2009.03.021. PMID: 19473786

Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011 Apr 6;305(13):1315-21. Also available: http://dx.doi.org/10.1001/jama.2011.370. PMID: 21467284

Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS, Stewart WF. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. Addiction. 2010 Oct;105(10):1776-82.

Campbell G, Nielsen S, Larance B, Bruno R, Mattick R, Hall W, Lintzeris N, Cohen M, Smith K, Degenhardt L. Pharmaceutical opioid use and dependence among people living with chronic pain: associations observed within the pain and opioids in treatment (POINT) cohort. Pain Med. 2015 Sep 1;16(9):1745-58. Also available: http://dx.doi.org/10.1111/pme.12773.

Dunn KM, Saunders KW, Rutter CM, BantaGreen CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med. 2010 Jan 19;152(2):85-92. PMID: 20083827

Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. Clin J Pain. 2014 Jul;30(7):557-64. Also available: http://dx.doi.org/10.1097/AJP.0000000000000021. PMID: 24281273

Huffman KL, Shella ER, Sweis G, Griffith SD, Scheman J, Covington EC. Nonopioid substance use disorders and opioid dose predict therapeutic opioid addiction. J Pain. 2015 Feb;16(2):126-34.

Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender differences in risk factors for aberrant prescription opioid use. J Pain. 2010 Apr;11(4):312-20.

Kaplovitch E, Gomes T, Camacho X, Dhalla IA, Mamdani MM, Juurlink DN. Sex differences in dose escalation and overdose death during chronic opioid therapy: a population-based cohort study. PLoS ONE. 2015 Aug 20;10(8) Also available: http://dx.doi.org/10.1371/journal.pone.0134550.

Liang Y, Turner BJ. Assessing risk for drug overdose in a national cohort: role for both daily and total opioid dose? J Pain. 2015 Apr;16(4):318-25. Also available: http://dx.doi.org/10.1016/j.jpain.2014.11.007. PMID: 25486625

Shah RD, Cappiello D, Suresh S. Interventional procedures for chronic pain in children and adolescents: a review of the current evidence. Pain Pract. 2016 Mar;16(3):359-69. Epub 2015 Mar 6. Also available: http://dx.doi.org/10.1111/papr.12285.

Turner BJ, Liang Y. Drug overdose in a retrospective cohort with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: interactions with mental health disorders. J Gen Intern Med. 2015 Aug 28;30(8):1081-96. Also available: http://dx.doi.org/10.1007/s11606-015-3199-4.

Turner JA, Saunders K, Shortreed SM, LeResche L, Riddell K, Rapp SE, Von Korff M. Chronic opioid therapy urine drug testing in primary care: prevalence and predictors of aberrant results. J Gen Intern Med. 2014;29(12):1663-71. Also available: http://dx.doi.org/10.1007/s11606-014-3010-y.

Zedler B, Xie L, Wang L, Joyce A, Vick C, Kariburyo F, Rajan P, Baser O, Murrelle L. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. Pain Med. 2014 Nov;15(11):1911-29. Also available: http://dx.doi.org/10.1111/pme.12480. PMID: 24931395

Key Questions 3 and 4: What is the comparative effectiveness and safety of COT versus other treatment modalities? a.) What is the comparative effectiveness and safety of COT versus no opioid therapy or other treatment modalities for patients with a history of or current SUD?

Breivik H, Ljosaa TM, Stengaard-Pedersen K, Persson J, Aro H, Villumsen J, Tvinnemose D. A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naive to potent opioids. Scand J Pain. 2010 Jul;1(3):122-41. Also available: http://dx.doi.org/10.1016/j.sjpain.2010.05.035.

Cloutier C, Taliano J, O'Mahony W, Csanadi M, Cohen G, Sutton I, Sinclair D, Awde M, Henein S, Robinson L, Eisenhoffer J, Piraino PS, Harsanyi Z, Michalko KJ. Controlled-release oxycodone and naloxone in the treatment of chronic low back pain: a placebo-controlled, randomized study. Pain Res Manag. 2013 Mar-Apr;18(2):75-82. PMID: 23662289.

Farrar JT, Messina J, Xie F, Portenoy RK. A novel 12-week study, with three randomized, double-blind placebo-controlled periods to evaluate fentanyl buccal tablets for the relief of breakthrough pain in opioid-tolerant patients with noncancer-related chronic pain. Pain Med. 2010 Sep;11(9):1313-27. Also available: http://dx.doi.org/10.1111/j.1526-4637.2010.00939.x. PMID: 20807345.

Friedmann N, Klutzaritz V, Webster L. Efficacy and safety of an extended-release oxycodone (Remoxy®) formulation in patients with moderate to severe osteoarthritic pain. J Opioid Manag. 2011 May-Jun;7(3):193-202. Also available: http://dx.doi.org/10.5055/jom.2011.0062. PMID: 21823550.

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Hale M, Khan A, Kutch M, Li S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. Curr Med Res Opin. 2010 Jun;26(6):1505-18. Also available: http://dx.doi.org/10.1185/03007995.2010.484723. PMID: 20429852.

Hale ME, Laudadio C, Yang R, Narayana A, Malamut R. Efficacy and tolerability of a hydrocodone extended-release tablet formulated with abuse-deterrence technology for the treatment of moderate-to-severe chronic pain in patients with osteoarthritis or low back pain. J Pain Res. 2015 Sep 15;8:623-36 Also available: http://dx.doi.org/10.2147/JPR.S83930. PMID: 26396543.

Hyup Lee J, Lee CS. A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of the extended-release tramadol hydrochloride/acetaminophen fixed-dose combination tablet for the treatment of chronic low back pain. Clin Ther. 2013 Nov;35(11):1830-40. Also available: http://dx.doi.org/10.1016/j.clinthera.2013.09.017. PMID: 24183364.

Katz N, Kopecky EA, O'Connor M, Brown RH, Fleming AB. A phase 3, multi-center, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of Xtampza ER in patients with moderate-to-severe chronic low back pain. Pain. 2015 Dec;156(12):2458-67. Also available: http://dx.doi.org/10.1097/j.pain.0000000000000315. PMID: 26262828.

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Opioid Therapy for Chronic Pain Clinical Practice Guideline

Face-to-face Meeting Summary

Prepared for:

Veterans Health Administration, U.S. Department of Veterans Affairs, and U.S. Department of Defense

Submitted by:

The Lewin Group, Center for Comparative Effectiveness Research

May 5, 2016

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Meeting Overview

Purpose

In consultation with the Contracting Officer Representative (COR), Champions, and the Evidence-based Practice Guideline Work Group (EBPWG), the Lewin Team convened a three-and-a-half day face-to-face meeting of the Opioid Therapy (OT) for Chronic Pain Clinical Practice Guideline (CPG) Work Group. The meeting was held at the Veterans Health Administration (VHA) National Conference Center in Crystal City, Virginia, from April 5 – 8, 2016. This Work Group comprised experts and other key clinical leaders from VHA and Department of Defense (DoD).

Under the direction of the Champions, the CPG Work Group utilized the available evidence, which was synthesized in an exhaustive report, to develop recommendations in order to generate the first draft of the clinical practice recommendations for the updated CPG for OT for Chronic Pain.

Participating Project Leadership and Contractor Staff

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	Pharmacy	
	Addictive Disorders, Psychiatry	
	Pain Medicine, Physical Medicine and Rehabilitation	
	Family Medicine, Primary Care	
	Pain Psychology	
	Internal Medicine, Addiction Medicine, Mental/Behavioral Health	
	Pain Medicine, Neurology, Clinical Neurophysiology	
	Palliative Care, Geriatrics	
	Nursing, Primary Care, Pain Medicine	

Name	Specialty	Location
Department of Defense		
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	Nursing, Medical Management	US Army Medical Command Fort Sam Houston, TX
	Pharmacy	Walter Reed National Military Medical Center/ Defense Health Agency Bethesda, MD
	Family Practice	Office of Evidence-Based Practice, US Army Medical Command, Fort Sam Houston, TX
	Family Medicine, Pain Medicine	Madigan Army Medical Center Joint Base Lewis-McChord, WA
	Social Work	Walter Reed National Military Medical Center Bethesda, MD
	Pain Management	Walter Reed National Military Medical Center Bethesda, MD
	Pharmacy	Defense Health Agency, Pharmacy Operations Division San Antonio, TX
	Psychology	Malmstrom Air Force Base, MT
	Physical Therapy	Walter Reed National Military Medical Center/ Defense Health Agency Bethesda, MD
	Pain Medicine, Anesthesiology	Marine Special Operations Command Camp Lejeune, NC

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